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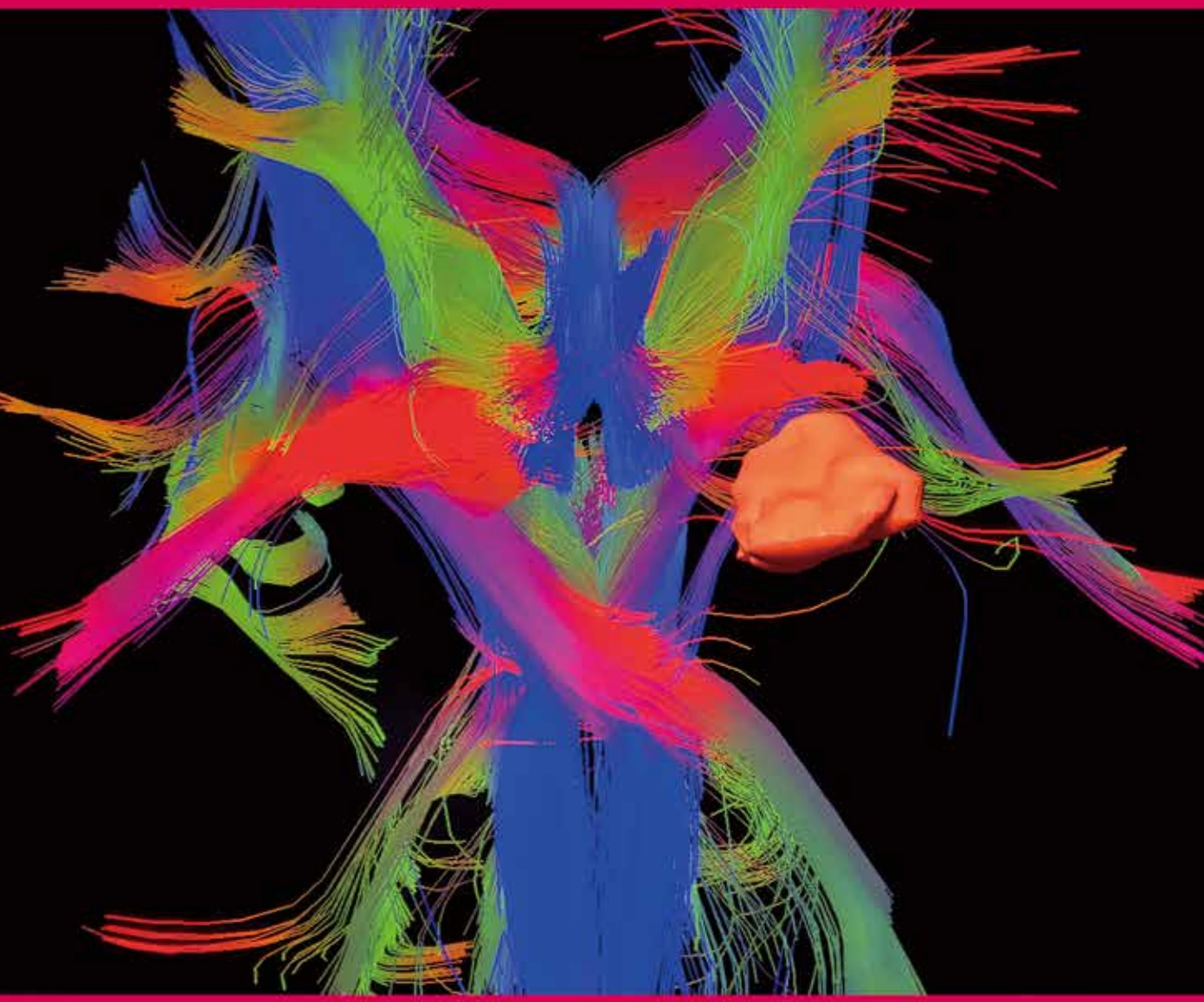

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Abbreviations: LUTS, lower urinary tract symptoms; OAB, overactive bladder

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Abbreviated prescribing information of Betmiga® prolonged-release tablets

Version: 003-Composition: Mirabegron **Indication:** Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome. **Dosage:** Adult including elderly 50 mg once daily with or without food. **Administration:** Swallow whole with liquids. Do not chew/divide/crush. **Contraindications:** Mirabegron is contraindicated in patients with: - Hypersensitivity to the active substance or to any of the excipients - Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg. **Special warnings and precautions for use:** Renal impairment: Betmiga has not been studied in patients with end-stage renal disease (GFR < 15 mL/min/1.73 m²) or patients requiring haemodialysis and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Betmiga is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors. Hepatic impairment: Betmiga has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. Betmiga is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors. Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline, and periodically during treatment with Betmiga, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg). Patients with congenital or acquired QT prolongation: Betmiga, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in post-marketing experience. In patients taking mirabegron, A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Betmiga; however, Betmiga should be administered with caution to patients with clinically significant BOO. Betmiga should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB. **Undesirable effects:** Summary of the safety profile: The safety of Betmiga was evaluated in 8,439 patients with OAB, of which 5,648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 620 patients received Betmiga for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 66% of the patients completed treatment with Betmiga, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with Betmiga 50 mg during the three 12-week phase 3 double blind, placebo-controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 3% in patients receiving Betmiga 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving Betmiga 50 mg. The frequency of urinary tract infections was 5.9% in patients receiving Betmiga 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving Betmiga 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long-term) active-controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. List of adverse reactions: The table below reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. **Infections and infestations: Common:** Urinary tract infection. **Uncommon:** Vaginal infection, Cystitis **Psychiatric disorders: Not known (cannot be estimated from the available data):** Insomnia* **Eye disorders: Rare:** Eyelid oedema **Cardiac disorders: Common:** Tachycardia, **Uncommon:** Palpitation, Atrial fibrillation **Vascular disorders: Very rare:** Hypertensive crisis* **Gastrointestinal disorders: Common:** Nausea*, Constipation*, Diarrhoea* **Uncommon:** Dyspepsia, Gastritis **Rare:** Lip oedema **Skin and subcutaneous tissue disorders: Uncommon:** Urticaria, Rash, Rash maculer, Rash papulei, Pruritus **Rare:** Leukocytoclastic vasculitis, Purpura, Angioedema* **Musculoskeletal and connective tissue disorders: Uncommon:** Joint swelling **Reproductive system and breast disorders: Uncommon:** Vulvovaginal pruritus **Investigations: Uncommon:** Blood pressure increased, GGT increased, AST increased, ALT increased **Renal and urinary disorders: Rare:** Urinary retention* **Nervous system disorders: Common:** Headache*, Dizziness* *Observed during post-marketing experience **Full prescribing information is available upon request.**

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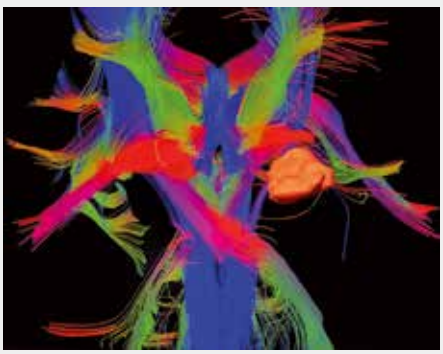
The Cover Shot



Human brain fibre tracking showing the white matter tracts from the front

This is a common image a neurosurgeon will face and study before operating on an intrinsic brain tumour (orange colour). It is very useful to import these data to the neuronavigation system so that the neurosurgeon can avoid damaging important fibres during surgery.

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Editorial

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Editor

Dr Michael WY LEE

This issue of the Hong Kong Medical Diary is the brainchild of a group of specialists in neurosurgery who contributed in their areas of interest and subspecialties with regard to the latest advances in neurosurgery. I would like to express my sincere gratitude to all the authors and everyone involved for their hard work and relentless support.

A connectome is a comprehensive map of neural connections in the brain, and may be thought of as the brain's "wiring diagram". The significance of the connectome stems from the realisation that the structure and function of the human brain are intricately linked, through multiple levels and modes of brain connectivity (from https://en.wikipedia.org/wiki/Connectome). Intraoperative neurophysiological monitoring utilises this piece of knowledge to safeguard the well-being and quality of life of the patients.

In acute stroke, a typical patient loses 1.9 million neurons each minute if it is left untreated. However, for proximal large-vessel occlusion (LVO) stroke, the rate of neuron loss per minute ranges from < 35,000 per minute in slow progressors to > 27 million per minute in fast progressors. The neuronal connectivity is definitely at stake and there is nothing more urgent than saving the brain with evidence-based therapies.

MRI-guided Focused Ultrasound Surgery (MRgFUS) provides novel incisionless treatment to functional neurosurgical disorders such as tremors. Aberrant neuronal tracts are disconnected and the connectome is restored to healthy status again. Besides, MRgFUS can open up the blood-brain barrier, and this may bring limitless opportunities in the treatment of tumours and dementia.

Endoscopic transorbital surgery utilises the openings in the skull as the access for connecting to the brain and this indeed opens a new chapter in brain and skull base surgery. Traditionally, neurosurgeons team up with ENT surgeons in advanced skull base surgery. Nowadays oculoplastic surgeons have become our new teammates.

As for the new armamentarium for the dreadful and lethal glioblastoma, Tumour Treating Fields (TTF) is the fourth modality in oncological treatment, in addition to maximal safe resection and chemoradiation. Good results are reproducible locally.

Smart Neurosurgical Operating Room in the New 5G Era shows us the immense potential of the internet of things (IoT) and how these connectivities help enhance productivity and safety.

Lovebirds are highly intelligent birds with complex relationships and needs. Some research suggested lovebirds have the same level of cognition as a 3-5-year-old child. It is a challenging task to take good care of these pets. And neurosurgeons love challenges.

Having combatted COVID-19 for more than two years, people are constantly practising isolation and quarantine. They are disconnected from the community, friends and relatives. Hope that we can be connected again soon.

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EXPERT VIDEO: FOOD FOR THOUGHT

Important brain nutrients throughout pregnancy and early childhood

How does nutrition modulate myelination?

WATCH FULL VIDEO NOW!

SPEAKER:
Dr. Gisella Mutungi
Senior Scientific Affairs Manager
Medical, Scientific and Regulatory Unit
Nestlé Nutrition, Switzerland

Examples of nutrients for the developing brain

Folic acid
-Folate deficiency leads to higher risks of neural tube defects in the embryo[1]

Choline
-Periconception choline intake may lower the risk of neural tube disorder[2]

DHA
-Neuron synaptic membranes showed higher concentrations[3]

Phospholipids (e.g. Sphingomyelin)
-Impact the pattern of developing myelination, favoring a later onset and a more prolonged rate of myelination[4]

LATEST RESEARCH: MYELINATION & DEVELOPING SOCIAL BRAIN

Exploring the relationship between myelin changes in social brain regions and changes in parent-rated social-emotional development

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Highlights

- **The first study investigating myelin changes in social brain areas** and how they relate to parent-rated social-emotional development
- Myelin development patterns within **the delineated social-emotional brain** revealed **a swift increase in myelination** during the first 2 to 3 years of life
- **The increase in myelination** was significantly associated with **social emotional development scores**

How does myelination relate to the growing brain?

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Intra-arterial Thrombectomy for Acute Stroke Management

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded 1 CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 April 2022.

INTRODUCTION

The paradigm of treating acute ischemic stroke has been revolutionised in the past two decades. Such drastic change is attributable to the concept of "penumbra" and its reperfusion.

When a blood vessel is blocked, the target tissue is hypo-perfused and it will eventually develop irreversible infarct. Such infarct occurs shortly in the 'central core', whereas the surrounding tissue is temporarily sustained by collateral blood supply.

This potentially salvageable tissue is known as 'penumbra'. Therefore, if blood supply can be restored in a timely fashion, this penumbra can be rescued and function can be preserved.[1]

2015 marked a major milestone in the development of acute stroke management, when clinical evidence became so strong that most major international stroke guidelines listed endovascular thrombectomy as class 1A recommendation for patients who fit the selection criteria. Another major breakthrough was in 2018, when evidence showed that the time window for safe and effective treatment could be extended to 24 hours in carefully selected patients. As a result, more patients can be rescued from the devastating consequences of major stroke.

EVOLUTION OF EVIDENCE

The first milestone in the modern era of stroke treatment was in 1995, when efficacy of intravenous recombinant tissue plasminogen activator (iv r-tPA) was proven in the National Institute of Neurological Disorders and Stroke (NINDS) r-tPA trial[2]. Stroke patients receiving r-tPA within 3 hours of onset were found to be at least 30% more likely to have minimal or no disability at three months. This time window was further extended to 4.5 hours in pooled data analysis from this and other related trials: ECASS I & II (European Cooperative Acute Stroke Study) and ATLANTIS A & B (Alteplase Thrombolysis for Acute Nonintervention Therapy in Ischaemic Stroke).[3,4]

However, for patients who suffered from stroke with large vessel occlusion (i.e. internal carotid artery, first and second segments of middle cerebral artery), recanalisation rate from iv r-tPA remained low and were reported to be 4 % and 30 % respectively.[5,6]

This led to the development of intra-arterial thrombolytic therapy, in which thrombolytic agents such as urokinase or tPA was instilled directly to the blocked cerebral artery by endovascular technique.

The PROACT II study[7] in 1999 proved that 40% of patients treated with intra-arterial pro-urokinase within 6 hours of MCA occlusion had good clinical outcome, with modified Rankin score (mRS) 2 or less, compared to 27% of the control group. However, the rate of symptomatic intracranial haemorrhage was also significantly higher (10% vs 2%), and the overall mortality was not significantly different.

DEVELOPMENT OF MECHANICAL THROMBECTOMY

Mechanical thrombectomy then gained its popularity in early 2000s. The first generation of FDA approved devices include MERCI Retrieval (Stryker, Kalamazoo, MI, USA) and Penumbra Stroke Systems (Penumbra Inc., Alameda, CA, USA). Their principle of action and details have been discussed in our previous review.[8]

However, three separate trials (IMS III[9], SYNTHESIS Expansion[10], and MR RESCUE[11]) published in 2013 showed that although both methods can achieve higher recanalisation rate, there was no significant improvement in clinical outcome when compared to patients managed with iv-tPA thrombolysis or standard medical therapy with anti-platelet drugs.

The focus was then switched to the next generation of devices termed 'stent retrievers', which are self-expanding, re-sheathable, re-constrainable stents mounted on microwire and deployed within the thrombus through microcatheter. The stent displaces the thrombus and presses it against the vessel wall so that blood flow is immediately restored. The clot is engaged by the stent struts and is removed when the stent is retrieved. Two commonly used stent retrieval devices are the Solitaire Flow Restoration Device (Medtronic Neurovascular, Irvine, California, USA) and Trevo retriever (Stryker Neurovascular, Fremont, California, USA). The Solitaire FR was found to have higher overall recanalisation rate when compared to the

MERCI results (89% vs 67%). Clinical outcome was also better as 58% of patients had mRS 0-2 at three months, compared to 33% in the control group.[12]

In 2015, 5 landmark randomised controlled trials were published: MR CLEAN[13], REVASCAT[14], ESCAPE[15], EXTEND-IA[16], and SWIFT PRIME[17]. These trials were conducted from 2010 to 2015 in Europe, the USA and Australia, where acute stroke patients with angiogram-proven large vessels occlusion in the anterior circulation were recruited. They unanimously demonstrated that patients treated with mechanical thrombectomy within 6 hours of stroke onset had improved recanalisation rates and significantly better clinical outcomes at 90 days.

Based on this, the American Heart Association (AHA)/ American Stroke Association (ASA) revised their guidelines in 2015 to support a Class 1A recommendation for using endovascular therapy with stent retriever in patients who meet the following criteria[18] :

a. Pre-morbid mRS score 0 to 1,
b. Causative occlusion of the ICA or proximal MCA (M1),
c. Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
d. Age ≥ 18 years,
e. Disabling stroke with NIHSS score of ≥ 6,
f. Small infarct size, Alberta Stroke Program Early CT Score (ASPECTS) of ≥6, and
g. Treatment can be initiated within 6 hours of symptom onset

A meta-analysis of these trials in 2016 showed that among those 1,287 eligible patients, 46% of those patients treated by endovascular thrombectomy had functional independence (mRS score 0-2) at 90 days, in contrast to 26.5% in the control group. The number needed-to-treat was 2.6 for one patient to have significant functional improvement. On the other hand, the rate of symptomatic intracranial haemorrhage and mortality rate between the intervention and control group were comparable (4.4% vs 4.3% and 15.3% vs 18.9% respectively).[19]

Some other important findings from these studies were that benefit of thrombectomy persisted regardless of stroke severity, whether the patient has received iv TPA, and across all age group including those older than 80 years old. In other words, old age is not considered as a contraindication if other eligibilty criteria are met.

Although the majority of patients in these trials were treated with the 'stent retrievers' system, another alternative technique is also available and has been proven to be equally effective.

A direct aspiration first pass technique (ADAPT)[20] involves a large-bore aspiration catheter which can be navigated to the proximal end of the occluding thrombus. The clot is engaged by applying continuous suction on the other end of the catheter, and then removed when the catheter is retrieved.

The first pass recanalisation success rate by this aspiration method is believed to be related to the calibre of the catheter. A number of choices of catheters is now available: Ace 64 and Ace 68 (Penumbra Inc., Alameda, California, USA), Sofia 6F (MicroVention, Aliso Viejo, California, USA), Catalyst 6 and 7 (Stryker Neurovascular, Fremont, California, USA) and Zoom 88TM (Imperative Care, Campbell, CA, USA).

Experience in multiple centres has shown that the 'puncture to re-vascularisation time' is shorter and the cost of device is less expensive. Patients receiving this ADAPT technique as first pass thrombectomy have been shown to have non-inferior functional outcome when compared to those having stent retriever.[21] In fact, a local survey revealed that the majority (83.3%) of our local interventionists adopted this as first-line thrombectomy technique.[22]

PATIENT SELECTION

While technological advancement has paved the way for successful endovascular treatment, careful patient selection remains a core determining factor.

The 2019 AHA/ASA stroke guidelines stated that patients with acute ischaemic stroke with symptom onset within 6 hours and fulfilling the above-mentioned criteria should undergo mechanical thrombectomy. It also advocated that either non-contrast CT brain or MRI brain can be used as an initial image study to exclude intracranial haemorrhage and to help assess extent of established infarct area.[23] In most centres, non-contrast CT is more easily available, bears lower cost and requires shorter study time.

The ASPECT (Alberta Stroke Program Early CT) score[24] provides simple and objective description of the infarct extent and help in predicting treatment response: The axial brain image in a CT is divided into 10 territories and one point is deducted for ischaemic change in each territory. A score lower than seven indicates a significantly extensive infarct and predicts a higher chance of haemorrhagic transformation after reperfusion therapy.

In addition to plain CT, CT angiogram or MR angiogram provides valuable information on the exact site and extent of large vessel occlusion. It can also show the presence of co-existing or 'tandem' lesion, and status of collateral circulation, which is a powerful indicator of outcome of such reperfusion therapy.[25]

FROM 6 to 24

The 2015 trials demonstrated improved functional outcome from mechanical thrombectomy, provided that treatment can be given within 6 hours of stroke onset.

In 2018, this treatment window was further extended to 24 hours by results of the DAWN and DEFUSE 3 trials.

The DAWN trial (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo)[26] used mismatch between the severity of neurological deficit (NIHSS) and infarct volume on diffusion-weighted image (DWI) in MRI or CT perfusion imaging (CTP) to select patients with large anterior circulation occlusion for receiving mechanical thrombectomy between 6 and 24 hours from symptom onset.

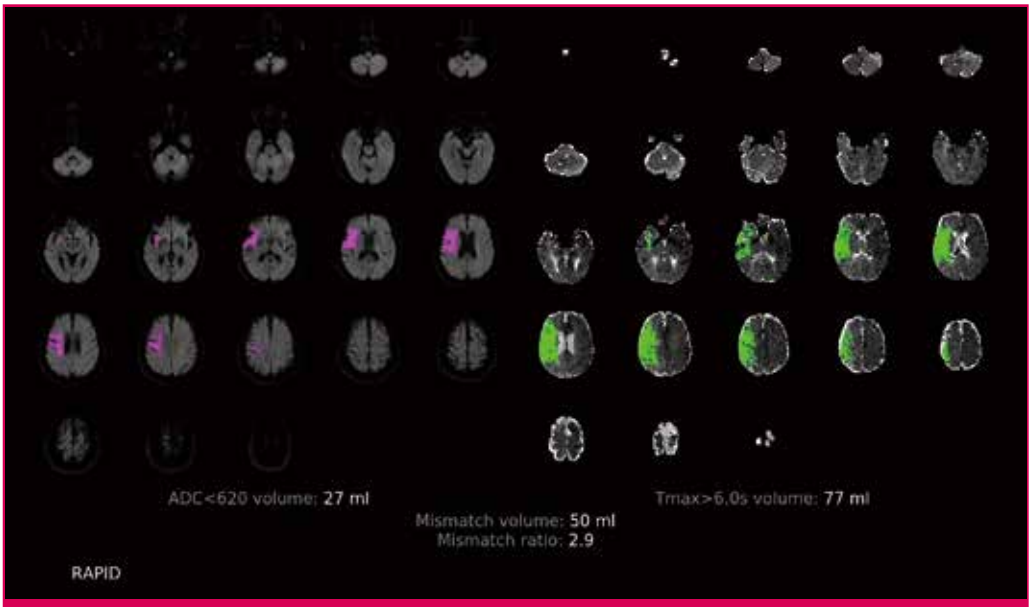

Fig. 1: MRI diffusion / perfusion image of a 60 year-old lady who presented with sudden onset of left side weakness. Pink shadow indicates area of established infarct, volume measured 27 ml; green shadow indicates area of hypoperfusion, volume measured 77 ml.
The mismatch volume (salvageable penumbra) is calculated to be 50 ml, mismatch ratio 2.9
(Personal collection)

At 90 days, 49% of patients who received mechanical thrombectomy plus standard care achieved mRS 0-2, compared to 13% of patients who received standard care alone.

The DEFUSE-3 trial (The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke)[27] selected patients who had an initial infarct volume less than 70 ml and a diffusion/perfusion mismatch ratio less than 1.8 for thrombectomy between 6 to 16 hours from last known normal. Image evaluation can be from CT perfusion or MR diffusion and perfusion scan, and calculated by automated software. (Fig. 1)

The percentage of patients who were functionally independent (mRS 0-2) at 90 days was 45% in the endovascular-therapy group, as compared with 17% in the medical-therapy group. On the safety issue, there was no significant difference in symptomatic haemorrhage between the two groups (7% vs 4%). 90 days mortality was 14% for thrombectomy group and 26% for the control.

Consequently, the AHA/ASA guidelines were revised in 2018 to provide class 1A recommendation for mechanical thrombectomy in selected patients who suffered from large vessel occlusion in anterior circulation (and met DAWN or DEFFUSE 3 criteria), and presenting within 6 -16 hours of last known normal; and class 2A recommendation in selected patients presenting in the 16-24 hours window.[28]

UNANSWERED QUESTIONS

One of the major unanswered questions is the actual benefit of thrombectomy for patients with posterior circulation (vertebra-basilar) infarct.

About 20 % of ischemic stroke belongs to this category, including acute basilar occlusion. While there is strong evidence to support endovascular therapy for acute ischemic stroke in the anterior circulation, data on such treatment for this group are still sparse. Currently, most of the results are from small centre series. The safe and effective time window is also unknown, though most believe that it should be longer than that in anterior circulation infarct. Nevertheless, given the fact that acute basilar occlusion will unavoidably end up with high morbidity and mortality in the range of 80-90%[29], most interventionists will agree to adopt a more aggressive treatment strategy.

A recently published systemic review analysed the pooled 1,612 patients who received mechanical thrombectomy for their posterior circulation stroke. Successful reperfusion was achieved in 86%. 38% of patients achieved good outcome at 3 months, and overall mortality rate was 30%. The authors concluded that additional studies are needed to identify favourable and modifiable indicators.[30]

Fig. 2a: Cerebral angiogram showed occluded right middle cerebral artery (Personal collection)
Fig. 2b: Perfusion in right middle cerebral artery recovered after thrombectomy with ADAPT technique (Personal collection)

CONCLUSION

Endovascular therapy is now considered standard of care for large vessel occlusion in the anterior cerebral circulation for selected patients. With advancement of image technology including CT perfusion scan, MR-DWI and MR-perfusion scan, the treatment window can be extended up to 24 hours in appropriately selected patients.

Prompt recognition by patients and / or their family, and timely transfer to specialised stroke centres that are capable of providing endovascular therapy service are of paramount importance in the management outcome, thereby improving stroke-related morbidity.

Keywords:
Acute ischemic stroke, endovascular therapy, intra-arterial thrombectomy

Abbreviations:
NIHSS- National Institute of Stroke Score

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MCHK CME Programme Self-assessment Questions

Please read the article entitled "Intra-arterial Thrombectomy for Acute Stroke Management" by Dr Kar-ming LEUNG and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded CME credit under the Programme for returning completed answer sheets via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 April 2022. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-10: Please answer T (true) or F (false)

1. **IAT is recommended as the standard of treatment for ischemic stroke presenting within 6 hours of symptom onset and caused by occlusion in the internal carotid artery or proximal middle cerebral artery.**
2. **The time interval between stroke onset and successful reperfusion is an important factor in determining the outcome.**
3. **The treatment window is now extended to 24 hours in selected patients.**
4. **Patients presenting beyond 6 hours of symptom onset should have CT perfusion or MRI diffusion/perfusion scan to determine if there is still salvageable brain tissue.**
5. **IAT should NOT be considered in patients older than 80 because there is no proven beneficial effect.**
6. **All patients suffering from acute vertebral or basilar occlusion are NOT suitable for IAT since the prognosis is grave anyway.**
7. **The rate of successful recanalisation by IAT is in the range of 50-70%.**
8. **CT or MRI brain is needed to exclude haemorrhagic stroke when IAT is considered for patients presenting with acute stroke symptoms.**
9. **In DAWN and DEFUSE 3 trials, patients had significantly higher rates or symptomatic intracranial haemorrhage after IAT.**
10. **Patients should be observed for at least 12 hours before transferring to designated stroke centres since the treatment window is now extended.**

ANSWER SHEET FOR APRIL 2022

Please return the completed answer sheet to the Federation Secretariat on or before 30 April 2022 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

Intra-arterial Thrombectomy for Acute Stroke Management

Dr Kar-ming LEUNG
MB.ChB, M.Med.Sc, FCSHK, FRCSEd, FHKAM (Surgery)
Specialist in Neurosurgery
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Name (block letters):_____ HKMA No.: _____ CDSHK No.: _____

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Contact Tel No.:_____ MCHK No. / DCHK No.: _____(must fill in)

Answers to March 2022 Issue

Pre-Exposure Prophylaxis on the Frontier of HIV Prevention

1. T 2. F 3. F 4. T 5. T 6. T 7. F 8. T 9. T 10. F

Updates in Intraoperative Neurophysiological Monitoring

Dr Michael WY LEE
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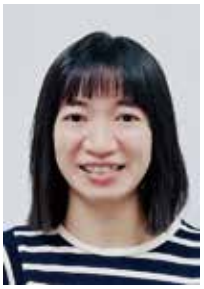

Dr Michael WY LEE Ms Shu-wah CHAU

Intraoperative neurophysiological monitoring (IONM) is an important tool in neurosurgery, aiming to enhance surgical safety, minimise postoperative neurological deficits, and preserve the quality of life of the patient. In particular, IONM is vital for skull base neurosurgery as there are many cranial nerves, tracts, and blood vessels traversing the surgical field. The goal of monitoring is to identify acutely impaired function along these pathways, alerting the surgeon so that prompt action can be taken to reduce or rectify the causes of such complications, hence substantially lessening postoperative neurologic sequelae.[1]

IONM requires an appropriate anaesthetic environment viz. stable blood pressure and core temperature, bispectral index level of 40-60, as well as avoidance of inhalation anaesthetic agents like halogenated agents or nitrous oxide, and neuromuscular blockade. Total intravenous anaesthesia (TIVA) is typically used. The operating theatre should be shielded from electrical noise, machines properly grounded and any dangling wires avoided. Irrigation solution on the operating table should be kept at body temperature, ideally with an automated warmer, and unnecessary cooling of neural tissue by exposure to room air should be avoided.[2]

Routine IONM in contemporary neurosurgery involves three most commonly employed evoked potentials (EPs) which are briefly summarised here.

SOMATOSENSORY EVOKED POTENTIAL (SEP)

Median nerve SEP begins with the delivery of a bipolar transcutaneous electrical stimulus to that nerve at the wrist. A 100–300μs square wave electrical pulse is delivered at intensities strong enough to cause a 1-cm thumb twitch. Nerve action volleys travel up sensory fibres and motor fibres to the shoulder, producing an N9 peak (Erb's point). The sensory fibres then traverse the cervical roots and enter the spinal cord, joining the posterior columns and sending off collateral branches to synapse in the midcervical cord, where the N13 negative peak, best measured over the fifth cervical spine, arises. Further conduction in the posterior columns passes through the synapse at the cervicomedullary junction and enters the lemniscal decussation, generating the P14 peak. As conduction continues up into the thalamus, a scalp negative peak N18 is detected. After synapsing in the thalamus and traversing the internal capsule, the N20 is recorded over the contralateral somatosensory cortex. Posterior tibial nerve stimulation at the ankle gives rise to a similar event with subsequent peaks detected: N8 potential at the knee, N22 potential over the upper lumbar spine, and finally, P37 potential over the midline scalp.

A significant SEP change is typically defined as a decrease in amplitude by half and prolonged latency for more than 1 ms from the baseline. In a meta-analysis of 5,607 patients for predicting postoperative neurological deficits[3], all significant SEP changes had a sensitivity of 44% and specificity of 97% with a diagnostic odds ratio (DOR) of 22.13. Reversible and irreversible SEP changes had sensitivities of 28% and 33%, specificities of 97% and 97%, and DORs of 13.93 and 57.84, respectively. Total loss of SEPs had a sensitivity of 9% and specificity of 99% with a DOR of 23.91. The specificity approaches 100% in all cases while the low sensitivity is explained by the fact that SEP is only good for monitoring the posterior column in the spine.

MOTOR EVOKED POTENTIAL (MEP)

MEPs are the electrical signals recorded from the descending motor pathways or from muscles following stimulation of motor pathways within the brain.[3] It can be direct stimulation of the exposed motor cortex, or transcranial stimulation of motor cortex, either magnetic or electrical.

For transcranial motor-evoked potential (TCMEP) monitoring, scalp screw electrodes deliver electrical stimulation of 100–600 V, with the duration of each train being 0.2 ms and the inter-pulse interval 2 ms. Surface electrodes or needle electrodes to record electromyographic (EMG) responses were placed on the abductor pollicis brevis (APB) and bilateral abductor hallucis (AH) muscles on the affected side in cranial operations and carotid endarterectomy. In spinal operations, electrodes were placed on potentially affected muscles according to their myotomes. To exclude the effects of muscle relaxants on TCMEP, compound muscle action potential (CMAP) by supramaximal stimulation of the peripheral nerve immediately after transcranial stimulation was used for compensation of TCMEP.

In spinal operations, with an 80% reduction in amplitude as the threshold for motor palsy, the sensitivity and specificity with CMAP compensation were 100% and 96.4%, respectively. In aneurysmal operations, with a 70% reduction in amplitude as the threshold for motor palsy, the sensitivity and specificity with CMAP compensation were 100% and 94.8%, respectively.[4]

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP)

The BAEP peaks are labelled with Roman numerals I-V. The succeeding peaks VI-VIII are quite variable, and are therefore not generally used clinically. The generators for waves I to V are the ipsilateral eighth cranial nerve (CN VIII), the ipsilateral cochlear nucleus, the contralateral superior olivary nucleus, the ipsilateral nucleus of the lateral lemniscus, and the contralateral inferior colliculus respectively.[5]

The I-III interpeak interval assesses conduction from the proximal CN VIII into the contralateral lower pons. This pathway can be impaired by tumours, inflammation, or other disorders affecting the pontomedullary junction where CN VIII enters the brainstem. It can also be disrupted as the pathway crosses through the lower pons, such as in central pontine myelinolysis. Usually, delays in the I-III interpeak interval are not considered clinically significant unless there is an accompanying prolongation of the I-V interpeak interval. The III-V interpeak interval reflects conduction from lower pons to the lower midbrain via the lateral lemniscus. This portion of the pathway is affected by intrinsic brainstem disorders such as tumours or demyelination.

BAEPs are elicited by broadband click stimuli with 100 dB sound pressure level (SPL) or 60–70 dB hearing level (HL). To mask crossover responses, white noise at 60 dB SPL or 30–35 dB HL is applied to the contralateral ear. Clicks can be of two polarities, either condensation or rarefaction, depending on the initial movement of the diaphragm of the transducer, and alternating click polarity may be useful to minimise stimulus artifacts. Recordings are made from the scalp vertex, with reference electrode at the ear ipsilateral to stimulation. Stimulus rates of 5-30 Hz with 500–1000 repetitions have been reported in the literature. The Korean group reported, using new machines, reliable waveforms at the rate of 43.9 Hz in an average of 400 trials. By obtaining a reliable BAEP in a shorter time, it is possible to detect CN VIII injuries faster during microvascular decompression (MVD) surgery, which can significantly reduce postoperative hearing loss (4.02% vs 0.39%, p =0.002).[6]

A 'sliding scale' protocol[6] for the critical warning signs of BAEP is suggested: 1) the attention sign: a latency prolongation of 1 ms without an amplitude decrement of at least 50%, 2) the warning sign: a latency prolongation of 1 ms with an amplitude decrement of at least 50%, and 3) the critical sign: a loss of wave V. The surgeon is notified immediately when there is attention sign, but no corrective manoeuvres are needed. The surgeon is again notified when the warning or critical sign appears, and aggressive measures to avert CN VIII injury are instituted when the critical sign occurs.

In specific skull base neurosurgery, there are newer IONM modalities depicted as follows:

Lateral spread response (LSR) in microvascular decompression (MVD) for hemifacial spasm

Conventionally, the temporal or zygomatic branch of the facial nerve, approximately 3 cm lateral to the lateral margin of the orbit, is stimulated for recording the LSR. The stimulating needle electrodes are inserted intradermally over the temporal or zygomatic branches of the facial nerve, and the direction of stimulation with paired needles is centripetal towards the brainstem, with the cathode positioned proximally. A 0.3-ms pulse wave with an intensity of 5 to 25 mA is used. The facial nerve EMG is recorded from the frontalis, orbicularis oculi, orbicularis oris, and the mentalis muscle. The interstimulus intervals (ISIs) of double stimulation range from 0.5 to 7.0 ms. R1 is defined as the response elicited by the first stimulus, and R2 as the response elicited by the second stimulus. R1 has a constant latency and amplitude regardless of the ISI, whereas R2 appears after a fixed refractory period without facilitation or depression in a recovery curve of latency and amplitude. Hence, the LSR is due to cross-transmission of facial nerve fibres at the site of vascular compression.[7]

Numerous studies have demonstrated a positive correlation between the intraoperative disappearance of LSR and favourable outcomes in patients undergoing MVD; therefore, LSR has been used as an indicator of complete facial nerve decompression. However, controversial findings, such as LSR absence before MVD or LSR persistence after MVD, have been reported. Furthermore, several studies suggested that residual LSR after MVD was not related to long-term outcomes.

Recently, a new LSR monitoring method[8] showed greater reliability. Preoperative LSR monitoring and mapping of the facial nerve branch allow stimulation of the facial nerve branch in the centrifugal direction. The anode is located proximally over the area just anterior to the mandibular fossa and the cathode distally in the temporal or zygomatic branch of the facial nerve (Fig. 1). This new method showed a significantly higher LSR disappearance after MVD (98.2% vs. 61.8%, p =0.0012), as well as significantly lower LSR persistence after MVD and LSR absence (1.8% vs. 29.1%, p =0.0051; 0.0% vs. 9.1%, p <0.0001, respectively).

Laryngeal adductor reflex (LAR) monitoring in posterior skull base neurosurgery

LAR is a vago-vagal reflex crucial for airway protection and prevention of aspiration. Dysphonia is related to dysfunction of the superior laryngeal nerve (SLN) and recurrent laryngeal nerve (RLN) innervating the cricothyroid, abductors and adductors. The neuronal basis of LAR[10] involves ipsilateral nucleus ambiguus at the medulla. SLN crosses at nucleus tractus solitarius at the reticular formation of the brainstem, via the contralateral nucleus ambiguus to form the crossed adductor reflex via contralateral RLN.

Conventionally, thyroid or parathyroid surgery utilises monopolar stimulation of RLN for vocal cord EMG

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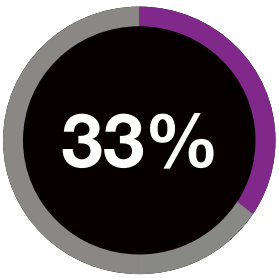

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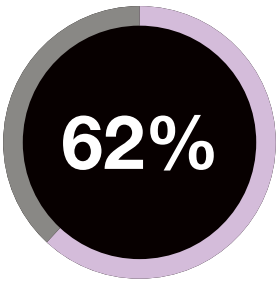

...of wrist and finger spasticity patients reported improvements toward their functional goals at Week 6 (n=64, p<0.001 versus placebo)[3]

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1. BOTOX Prescribing Information May 2013. 2. Gordon MF, et al. Neurology. 2004;63(10):1971-1973 3. Brashear A, et al. N Engl J Med. 2002;347(6):395-400.

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For vertical muscles and for horizontal Strabismus of less than 20 prism diopters (PD): 1.25 to 2.5 U in any one muscle. B. For horizontal strabismus of 20 to 50 PD: 2.5 to 5.0 U in any one muscle. C. For persistent VII nerve palsy of one month or longer duration: 1.25 to 2.5 U in medial rectus muscle. Blepharospasm 1.25 to 2.5 U (0.05 to 0.1 mL volume at each site) injected into medial and lateral pre-tarsal orbicularis oculi of upper lid and into lateral pre-tarsal orbicularis oculi of lower lid. VII Nerve Disorders (Hemifacial Spasm) should be treated as for unilateral blepharospasm. Cervical Dystonia (Spasmodic Torticollis) Dosing must be tailored to the individual based on the patient's head and neck position, localisation of pain, muscle hypertrophy, patient's bodyweight, and patient response. Type I (Head rotated toward side of shoulder elevation), injection to Sternocleidomastoid (50-100 U; at least 2 sites), Levator scapulae (50 U; 1-2 sites), Scalene (25-50 U; 1-2 sites), Splenius capitis (25-75 U; 1-3 sites), Trapezius (25-100 U; 1-8 sites). Type II (Head rotation only), injection to Sternocleidomastoid (25-100 U; at least 2 sites if >25 U given). Type III (Head tilted toward side of shoulder elevation), Sternocleidomastoid (25-100 U; at posterior border; at least 2 sites if >25 U given), Levator scapulae (25-100 U; at least 2 sites), Scalene (25-75 U; at least 2 sites), Trapezius (25-100 U; 1-8 sites). Type IV (Bilateral posterior cervical muscle spasm with elevation of the face), injection to Splenius capitis and cervicis (50-200 U; 2-8 sites, treat bilaterally) Spasticity in Juvenile Cerebral Palsy Patients (≥2 years old) 4 U/kg administered by injecting 2 cc of reconstituted BOTOX® into each of two sites in medial and lateral heads of gastrocnemius muscle of the affected lower limb(s). Primary Hyperhidrosis of the Axillae 50 U of BOTOX® (2.0 mL) is injected intradermally to each axilla in multiple sites. Focal Spasticity associated with Stroke in Adults The exact dosage and number of injection sites should be tailored to the individual. In controlled Phase 3 clinical trial, following doses were used: flexor digitorum profundus(50 U), flexor digitorum sublimis(50 U), flexor carpi radialis(50 U), flexor carpi ulnaris (50 U), adductor pollicis(20 U), flexor pollicis longus(20 U). In all clinical trials, the doses did not exceed 360 U divided among selected muscles at any treatment session. Chronic migraine Intramuscularly (IM) injections of 0.1 mL (5 U) to 31 up to 39 sites, across 7 areas: frontalis(20 U), corrugator(10 U), procerus (5 U), occipitalis (30 to 40 U), temporalis(40 to 50 U), trapezius(30 to 50 U), cervical paraspinal Muscle Group (20 U). Bladder Dysfunction Detrusor Overactivity associated with a Neurologic condition: 30 injections of 1mL (≈6.7 U) each, with total 200 U/30mL into detrusor muscle. Overactive Bladder: 20 injections of 0.5mL (5 U) each, with total 100 U/10mL into detrusor muscle. **Contraindications:** Individuals with known hypersensitivity to any ingredient in the formulation. Patients with myasthenia gravis or Eaton Lambert Syndrome. BOTOX® is contraindicated in the presence of infection at the proposed injection site(s). 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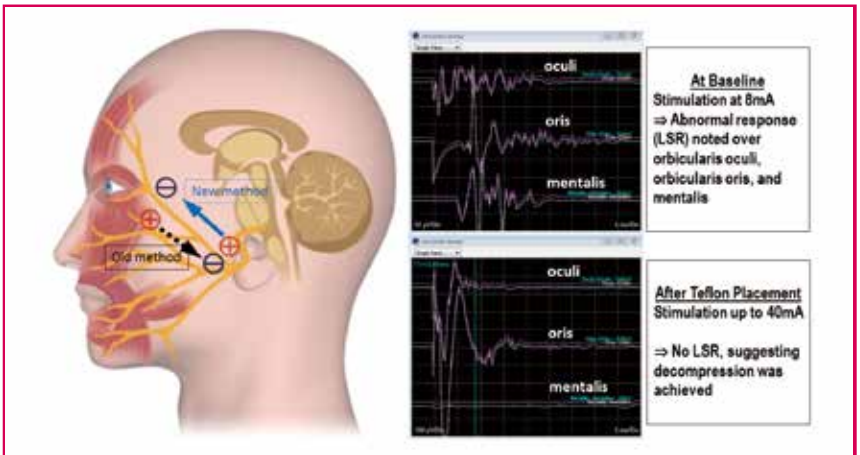

Fig. 1: For the old or conventional method for LSR, centripetal impulses are transmitted towards the brainstem with the cathode positioned proximally. For the new method, the stimulation direction is centrifugal outward from the brainstem with anodal intradermal electrodes located proximally and the cathodal distally.[9] (Adapted from Lee S, Park SK et al.[8,9]) Right upper and lower graphs showed the presence and absence of LSR before and after decompression. (Clincal photos from personal collection)

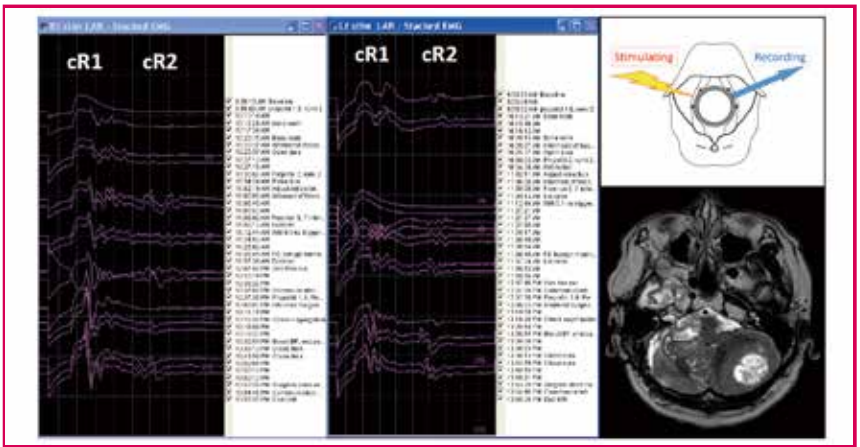

Fig. 2: Posterior fossa papillary meningioma (WHO grade III) encasing brainstem and lower cranial nerves. Total excision was performed without vocal cord deficits. Bilateral cR1 and CR2 remained stable during surgery. (Personal collection) Right upper diagram shows the endotracheal tube with EMG electrodes between vocal cords. (Personal collection)

response. Besides, triggered vocal cord EMG response is obtained from direct stimulation of vagus nerve in brainstem surgery as well as stimulation of the corticobulbar tract via TCMEP.

New method of LAR monitoring[11] utilitses ET tube with surface-based electrode, with stimulation of contralateral side vocal cord and recording over ipsilateral vocal cord for crossed response cR1 and cR2 waves. Contralateral cR1 and cR2 responses are obtained from stimulating ipsilateral vocal cord using single stimulus of pulse width 200 μs with stimulating intensity 2 to 10 mA, and repetition rate of 3.1 Hz. Recording parameters are time sweep of 100 ms and amplification of 100 μV with bandpass of 30-3k Hz. The warning criteria is a reduction in LAR amplitude by 60%.

Using these settings that allow continuous IONM, a prospective multi-centre pilot study in Hong Kong[12] from November 2017 to November 2019 involving 29 patients with large posterior fossa lesion (mean tumour volume 23.25cm^3) affecting lower brainstem, IONM was able to detect postoperative vocal cord deficits with a sensitivity and specificity of 75% and 92% respectively. The positive and negative predictive values were 60% and 95.83% respectively. The Area Under the Curve (AUC) was 0.86 (good category). This is comparable to the conventional monitoring in thyroid and parathyroid surgeries with 1,381 nerves at risk[13]. The false positive (loss of signal with intact vocal mobility) could be explained by technical issues on the stimulation or recording side, such as vertical or rotational ET tube displacement, ''salt-bridging'' phenomenon related to progressive salivary pooling at the glottis, and stimulation suppression artefact eliminating early responses.

Further update in our local data in 46 patients showed that the sensitivity and specificity were 86% and 95% respectively. The positive and negative predictive values improved to 75% and 97% respectively.

BLINK REFLEX (BR) MONITORING

BR is a an electrical analogue of the clinically elicitable corneal reflex (Fig. 3). Direct stimulation produces a CMAP of the facial nerve, with two components, R1 and R2. The early R1 response is relatively synchronous and constant in duration and shape, and the response only slowly drops with repetitive stimulation. The second response R2 is a late bilateral response which corresponds to the clinically observable blink. The latter response is asynchronous, and it rapidly habituates and disappears bilaterally. Compressive lesions of trigeminal nerve, such as tumours or aneurysms, involve the afferent limb of the reflex arc and prolong the latency of ipsilateral R1 and bilateral R2. Facial nerve lesions affect the efferent limb of the blink reflex arc and delay the latency of ipsilateral R1 and R2. In the lateral medullary syndrome (Wallenberg's syndrome), both ipsilateral and contralateral R2 are abnormal when the affected side is stimulated, while stimulation of the normal side produces a normal response. For pontine lesions R1 component has been reported abnormal, unilaterally or bilaterally. In comatosed states, R2 response is non-elicitable on both sides.

Recording electrodes are placed over the orbicularis oculi muscle at the lower eyelid. A reference electrode is placed over the orbicularis oculi muscle on the lateral aspect. The right and left supraorbital nerves are stimulated electrically at the supraorbital notch. A stable R1 response on both sides is elicited using a train-of-four constant-current stimuli with an interstimulus interval of 2 ms, 300 μs pulse width and intensity of up to 40 mA at our hospital. Recording parameters are time sweep of 50 ms and amplification of 25-50μV with a bandpass of 10-3k Hz. As previously reported, R2 response was not elicitable under general anaesthesia.[15]

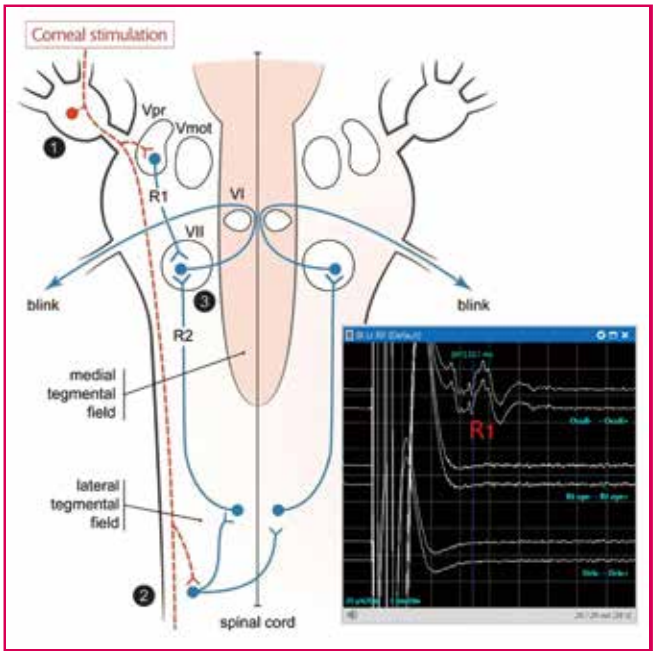

Fig. 3: Schematic representation of the corneal reflex pathway in relation to the blink reflex pathways (R1, R2). (Image courtesy of Maciel CB, et al.[14]) The left corneal stimulus is perceived by the supraorbital nerve ❶ and conducted to the trigeminal motor nucleus where the ipsilateral R1 response is obtained via an oligosynaptic arc to the CN VII nucleus. This response is not visible clinically. The supraorbital nerve also conducts the afferent impulse through the descending spinal tract of the trigeminal nerve in the lower brainstem (pons and medulla) to the caudal spinal trigeminal nucleus ❷ (dotted orange line demarcates the afferent pathway). The efferent impulse (full blue line) is conducted via the medullary pathway that ascends bilaterally to connect to the facial nuclei (pons) ❸ and yields the R2 responses which are clinically apparent through the blinking response. VII = facial nucleus. VI = abducens nucleus. Vpr = principal trigeminal nucleus. Vmot = trigeminal motor nucleus. Right lower graph shows the typical R1 response elicited during BR IONM. R2 response is not elicitable under general anaesthesia. (Personal collection)

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Endoscopic Transorbital Approach to Skull Base (ETOA) – The Past and Beyond

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INTRODUCTION

With the advances in microscopic and endoscopic instruments in neurosurgery, surgeons are more aware of minimising the morbidities and invasiveness of skull base surgeries. Examples would be endoscopic transsphenoidal surgeries and keyhole approaches to the skull base. The endoscopic transorbital approach (ETOA) to skull base offers another minimally invasive and versatile route to tackle deep-seated skull base lesions. Kris Moe, an ENT surgeon, first introduced the approach in June 2007, and his first case series was published in 2010.[1] The concept is to provide another corridor for laterally placed anterior skull base lesions or paramedian lesions that cross neurovascular structures, which could not be addressed by endoscopic endonasal surgeries alone. It is estimated that the central portion of ventral anterior cranial fossa bounded laterally by orbits occupies around 20% of the anterior skull base, where the central ventral anterior skull base can be accessed via the endonasal route without crossing critical neurovascular structures. As the orbits occupy the remaining 80%, access to this area via the endonasal route would inevitably cross neurovascular structures.[1] ETOA provides a direct anterior approach to skull base lesions lateral to the cavernous segment of the internal carotid artery (ICA), requires minimal bony removal, and achieves better cosmetic results. Incorporating refined microscopic and endoscopic instruments also provide excellent illumination and magnification.

SURGICAL METHODS

Step 1: Skin incision

The first step of the operation starts with the planning of the skin incision. We cooperate with oculoplastic surgeons for optimal planning and minimising wound complications. A wide variety of wounds have been described in the literature. In essence, the orbit can be approached superiorly, inferiorly, laterally, or medially. Fig. 1a is an example of a lid crease incision. After the skin incision, the orbicularis oculi muscle is divided, and the periosteum is stripped. Orbitotomy can be performed to increase the working angles and surgical freedom.

Step 2: Drilling of greater sphenoid wing

After the skin incision, the periorbita is stripped away from orbital walls. The endoscope is introduced, and drilling of the greater sphenoid wing is performed with a high speed drill with self-irrigation system. Copious irrigation is important to prevent thermal injuries to orbital content. Oculoplastic surgeons also help to minimise traction on the orbit. It has been shown that orbital compression of more than 1.5cm is associated with a dramatic increase in intraocular pressure.[3] After drilling the sphenoid wing, the meningo-orbital is exposed and divided to unlock the anterior and middle cranial fossa (Fig. 1b).

Step 3: Extradural dissection-peeling of the cavernous sinus

Once the dura of the anterior and middle fossa is separated, peeling of the lateral cavernous wall was performed extradurally to exposure the trigeminal nerve (Fig. 1c). This step is similar to the extradural peeling of the cavernous sinus in craniotomy. Anteromedial triangle is the triangle formed between the ophthalmic division (V1) and maxillary division of trigeminal nerve (V2), whereas an anterolateral triangle is a triangle between V2 and mandibular division of trigeminal nerve (V3)(Fig. 1d). These two triangles serve as an important landmark to guide entrance into the cavernous sinus, infratemporal fossa, and petrous apex.

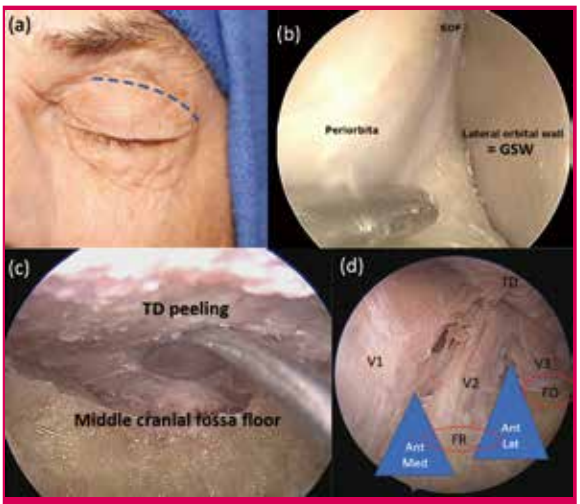

Fig. 1 (a)-(d): (a) Left eyebrow transciliary incision. (b) Stripping of periorbita from greater sphenoid wing (GSW) with exposure of superior orbital fissure (SOF). (c)Temporal dura was peeled from the middle cranial fossa floor. (d) Anteromedial triangle (Ant Med) between V1 and V2 and anterolateral triangle (Ant Lat) between V2 and V3 were exposed with V2 entering foramen rotundum (FR) and V3 entering foramen ovale (FO) (Personal Collection, Cadaveric Dissection)

INDICATIONS

Only a limited number of cases have been reported in the literature. The most common indications are cerebrospinal fluid (CSF) leak repair and excision of skull base tumours.

The most common causes of CSF leak repaired via transorbital route include iatrogenic and traumatic CSF leaks. The majority of leakage sites were in the anterior cranial fossa and repaired via an endoscopic transorbital approach.[2]

For tumour excision, the most common indications are excision of spheno-orbital meningiomata and middle fossa schwannomas. The transorbital approach alone has been used in the majority of cases, while combined transorbital and endonasal approaches have been used in the others. The overall mean length of stay was around three days in the cases reported.[2]

In a recent case series by Kong et al. comparing ETOA and ETOA with lateral orbitotomy, the lateral orbitotomy group had a better gross total excision rate for spheno-orbital meningioma.[8] In our experience, lateral orbitotomy could contribute to greater surgical freedom and minimise retraction-related morbidities.

Other reported indications include cavernous haemangioma, intracranial abscesses, fibrous dysplasia, frontal mucocele, and fibroxanthoma.[2,5]

SURGICAL OUTCOMES

ETOA is very effective in repairing CSF leaks, with a success rate ranging from 83% to 100% and a recurrence rate of 7%. On the other hand, the gross total excision rate for transorbital tumour surgeries is around 70%. For those patients with preoperative neurological deficits, including limited extraocular eye movements (EOMs), impaired visual acuity, proptosis, and ptosis, most of them improved after surgeries.[2]

COMPLICATIONS

In a recent systematic review of ETOA by the Barrow Neurological Institute, the reported complication rate was 13%.[2] Nearly all complications were transient except for a case of permanent proptosis. The most common complication is CSF leak, accounting for 66.7%. It is usually transient and seldomly requires repair. After transorbital surgery, our group repairs the skull base defects with dura substitute, tissue glue, and occasionally abdominal fat graft. No CSF leak has even been experienced in our clinical collection of over 15 patients so far.

Reported temporary neurological deficits include diplopia, facial numbness, and ptosis.

Other reported complications include levator muscle dysfunction, meningitis, periorbital hematoma, epiphora, superficial surgical site infection, and orbital pseudomeningocele.[6]

DISCUSSION

Since the first publication of the transorbital case series, there has been limited evidence comparing surgical outcomes between transorbital surgeries and traditional approaches such as craniotomies. Most of the publications are anatomical studies and case series. In our centre, we started performing ETOA in 2020. With the collaboration with oculoplastic surgeons, ETOA achieves a better cosmetic result as only a small incision along natural skin creases is made. Cosmetic outcome is also better for proptosis correction. There is less blood loss and no brain retraction compared to craniotomies. It avoids atrophy of temporalis muscle and injury to the frontal branch of the facial nerve. There is also a low chance of CSF leak compared to the endonasal approach.

Furthermore, ETOA can also be combined with other operative corridors, such as endonasal and transoral routes. Through entering and traversing operative corridors in anterior and middle cranial fossa, ETOA provides an excellent view of important neurovascular structures with the help of angled endoscopes. Important cranial nerves and great vessels can be protected via ETOA to facilitate the removal of lesions via ETOA alone or in combination with other endoscopic routes.[4,7] A panoramic view of the anterior and middle cranial fossae can be made possible through pure endoscopic minimally invasive approaches.

Cadaveric dissection and the formation of a multi-disciplinary team remain the essential components to start performing ETOA. ETOA is a novel technique; the anatomy in this procedure may be disorientating to surgeons. Cadaveric dissection and anatomical studies are the best ways to allow the surgeons to get familiarised with the operative anatomy. Oculoplastic surgeons and ENT surgeons can share their expertise in minimising ocular morbidities and in handling difficult head and neck tumours, thus optimising surgical safety and patient outcomes.

CONCLUSION

ETOA provides a direct anterior approach to the orbital apex and skull base pathologies lateral to the cavernous sinus and at the infratemporal fossa. As this is minimally invasive in nature, it has the potential for biportal or even triportal surgeries. Thorough understanding of the anatomy via cadaveric dissection in the laboratory, and multi-disciplinary collaboration are key elements of success to start this novel procedure.

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Incisionless Neurosurgery - MRI-guided Focused Ultrasound Surgery

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BACKGROUND

MRI-guided focused ultrasound (MRgFUS) surgery is a non-incisional, thermal ablation method that integrates High Intensity Focused Ultrasound (HIFU) and Magnetic Resonance Imaging (MRI) as a therapy delivery system. The Hospital Authority (HA) is the pioneer in Hong Kong planning to introduce MRgFUS treatment service, tentatively in 2023, after the installation of the equipment in the new operation theatre extension block of Tuen Mun Hospital. Patients with medication-refractory Essential Tremor (ET) (the only indication in HK at the time of this publication) have been approved by the HA to be potential candidates for this novel treatment option.

INTRODUCTION

HIFU has been widely used to treat patients with prostate cancer, thyroid nodules, breast fibroadenomas, renal tumours and liver tumours. Coupling with MRI-guidance, HIFU is also used for the treatment of symptomatic uterine fibroids[1] and painful osseous metastases.[2]

However, due to the complexity of the central nervous system and also the solid skull, the brain was an unreachable target by HIFU until 2016, when Elias et al. published their randomised trial of focused-ultrasound thalamotomy for ET in the New England Journal of Medicine. In the same year, Transcranial MRgFUS (tMRgFUS) treatment was approved by the US Food and Drug Adminstration (FDA)for clinical use.

MECHANISM OF ACTION- THERMAL LESIONING, MECHANICAL DISRUPTION, NEUROMODULATION

The tMRgFUS system delivers ultrasonic energy to the brain across an intact skull.[3] It delivers up to 1,024 ultrasound waves to precisely ablate a target deep in the brain without incisions or implants.

Apart from thermal lesioning, the ability of tMRgFUS to temporarily disrupt the blood-brain barrier (BBB) has been shown in a preclinical study.[4] With or without the combined use of microbubbles and ultrasonic waves, tMRgFUS temporarily alters the vascular or cell membrane permeability in the brain. Various compounds could then be released or activated for targeted drug delivery or gene therapy to the brain.

tMRgFUS can also be used for its non-thermal mechanical effects (e.g. mechanical disruption of blood clots) and for its non-thermal non-mechanical effects on the excitability of brain cells (i.e. neuromodulation).

The above capabilities of tMRgFUS have given rise to the potential to revolutionise not only functional neurosurgery[5] but also the neurosurgical and pharmacological treatment of brain tumours.

CLINICAL APPLICATION

Although medication-refractory ET is the only indication approved by the Hospital Authority of Hong Kong, the indication list for this cutting-edge technology has been expanding. Central neuropathic pain[6,7], movement disorders (ET[8], Tremor Dominant Parkinson's Disease (TDPD)[9]), brain tumours[10] and psychiatric illnesses (major depressive disorder (MDD) and obsessive-compulsive disorder (OCD)) are some examples that have been deemed promising to be managed using MRgFUS.

FDA approved MRgFUS treatment for ET in July 2016 and TDPD in Dec 2018. The China National Medical Production Administration of Mainland China subsequently approved the above two indications in Feb 2021.

EQUIPMENT and TECHNOLOGY

The (ExAblate 4000, InSightec) system is integrated with an 3T or 1.5T MRI scanner.

Fig. 1: The transducer helmet is housed in a manually operated positioning system and is integrated into an MRI table (Excerpted from Insightec web page www.insightec.com)

The MRgFUS system consists of

1. A transducer helmet (30-cm diameter hemispheric 1024-element phased-array transducer operating at 650 kHz),
2. A treatment workstation
3. A front-end electronics unit
4. An equipment cabinet and a water circulation, cooling, and degassing system.

Fig. 2: Photograph (2A) and schematic depiction (2B) of the MRgFUS system (Excerpted from Insightec web page www.insightec.com)

Fig. 2A: Patient is fixated to imaging table by frame. The circulat elastic membrane holds water between the transducers and patient's head (Excerpted from Insightec web page www.insightec.com)

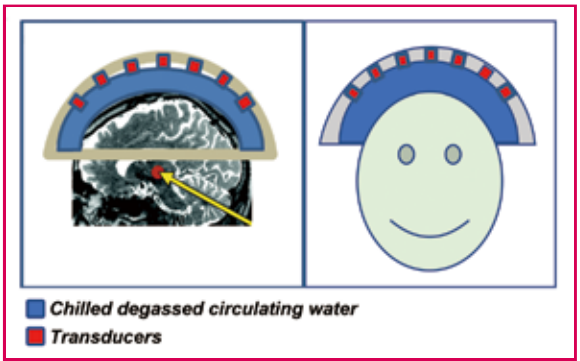

Fig. 2B: Water-tight membrane holds chilled, degassed circulating water between transducer and patient's head. The transducers can be moved independently to place target as closely as possible to geometric centre of the hemisphere. (Excerpted from Insightec web page www.insightec.com)

Ultrasound Focusing

As the transmission of ultrasound will be attenuated by the bony skull (20 times more than by soft tissue), mostly due to absorption, the risk of scalp skin burn and skull heating has to be tackled by

1. The transducer's design allows the delivery of low intensity ultrasound energy over a large area at the transducer surface.
2. Multiple energy beams intersect with the cranium at different locations, thus minimising focal heating on the skull.
3. Geometric convergence of the ultrasound beam results in a high-intensity focus inside the brain, while the intensity is relatively low at the skull.
4. Circulating chilled water around the head further ensures cooling of the cranium and adjacent soft tissues. Hair shaving and application of gel pad to the scalp are required to ensure water-tight application of the helmet to the patient.

Some loss of ultrasonic wave intensity occurs and is caused by reflections within the trabeculae of the bone and at the bone & soft tissue interface. The transparency of the skull to ultrasound is assessed by skull density ratio (SDR). A higher SDR allows more efficient delivery of energy to the brain. The procedure can be safely and effectively performed with an SDR of >= 0.3, although the procedure is more efficient when the SDR is >0.45.

The speeds of sound wave through soft tissue and bone are different. To make the situation worse, the heterogeneous thickness and density of different parts of the skull also alter the phases of individual ultrasound beams. (Fig. 3A).

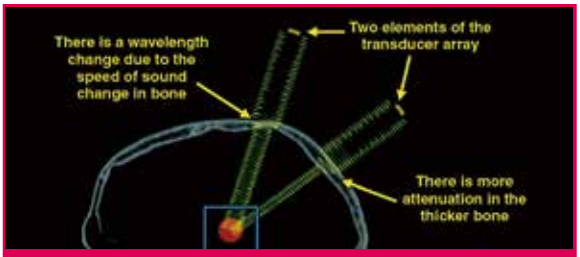

Fig. 3A and 3B: Wavelength change owing to different thickness of skull bone may cause cancelling out of ultrasound energy (Excerpted from Ghanouni et al. Applications of Transcranial MRI-Guided Focused Ultrasound. American Journal of Roentgenology 2015; 205:150–159)

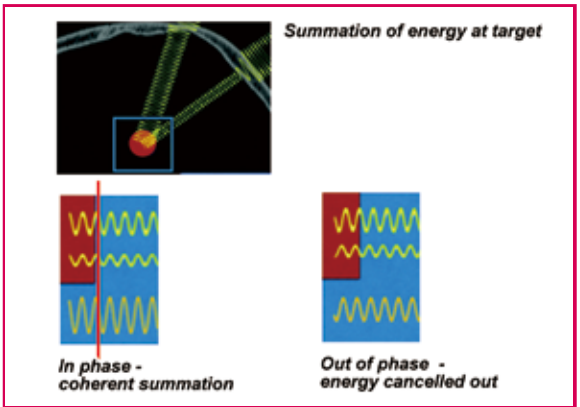

Fig. 3B: To ensure the beams are in phase, the phase change for each beam path through the skull is estimated and corrected for. A more coherent summation of energy at the target thus can be achieved.

Skull Density Ratio (SDR) and phase correction terms are estimated from a planning CT scan obtained prior to the treatment. The planning CT is fused to the MR image during the time of treatment.

Phase offsets can also be used to steer the beam over a few milimetres. If larger changes in target position are needed, the transducer can be physically moved, while the patient stays fixated by the head frame.

Although some degree of freedom in the positioning of the target is allowed by moving the transducer or electronic focusing, the treatment region is still limited to the centre of the brain. If the transducer is moved too much, the incidence angles of the beam on the skull will become too large. Reflections at these large incidence angles reduce the number of elements that can contribute effectively to the focal spot.

The skull base also poses limitation to the treatment envelope. Treatment too close to the skull base could result in excessive skull heating[11]. Therefore, lesions adjacent to the skull base and to the calvaria cannot currently be treated using MRI-guided FUS (e.g. in epilepsy surgery where the cortical seizure focus is close to the calvaria) .

Thermal MRI

The intensity of energy arriving at the target may vary among different patients because of a variety of factors including physical factors (such as skull thickness and density), technical factors (such as accuracy of the phase correction), and physiologic factors (such as tissue perfusion). As a result, in order to achieve effective ablation, temperature monitoring at the target spot is critical to verify accurate targeting and adequate heating.

Many MRI parameters change with temperature, including the T1 and T2 decay rates, the proton density, the diffusion coefficient and the proton resonance frequency.

The proton resonance frequency is the most commonly used parameter for monitoring temperature change because it is easily measurable, reversible and linear over the temperature range of interest.

Fig. 4: Real Time Thermal MRI monitoring (excerpted from Insightec web page www.insightec.com)

On imaging, the average resonance frequency in the voxels is reduced when the temperature increases. The change can be seen in the phase of gradient-echo images. The temperature-induced change can be isolated by subtracting the baseline image acquired before the temperature increase.

TREATMENT of MOVEMENT DISORDERS

Essential tremor

Movement disorders are often disabling conditions that interfere significantly with a patient's quality of life[12] and may be medically refractory. ET, also referred to as familial, idiopathic, or benign tremor, is the most common movement disorder, affecting more than 5 million people in the United States, and millions more worldwide, with an estimated incidence of 0.3–5.55%.[13-15]. Hand tremor is the most common symptom, but the head, arms, voice, legs, and torso can also be affected. For these patients, performing everyday tasks becomes a challenge.

When medications fail to offer relief, surgical intervention may be the next step. Medication-refractory ET can be addressed by ablating a specific nucleus of the thalamus (Ventralis Intermedius Nucleus (VIM)[8]). In pilot clinical trials of patients with ET conducted as early as in 2013, the VIM on the contralateral side of patients' dominant hand was ablated by tMRgFUS.[8,16,17]. Twenty out of the 30 study patients were successfully treated. With up to 12 months' follow-up in the largest trial, the studies reported significant improvements in tremor, disability, and quality of life.

Complications related to MRgFUS thalamotomy reported include paresthesias of the face or fingers, which persisted at 12 months in five of 19 patients; persistent dysesthesia of the index finger in 1 patient; and transient unsteadiness, ataxia, dysmetria, grip weakness, and slurred speech, all of which resolved within a month.

Approval by the FDA was based on a randomised, double-blind, multi-centre clinical study by Elias et al. in 2016. Designed to evaluate non-invasive thalamotomy with MRgFUS, a total of 76 patients were enrolled and randomly assigned to receive the treatment (56 patients) or the sham procedure (20 patients), the exact same procedure but without any ultrasound energy. Patients in the placebo treatment arm were later allowed to cross over to the real tMRgFUS treatment. It was found that patients treated with MRgFUS showed nearly a 50% improvement in their tremors and motor function three months after treatment compared to their baseline score. Patients in the control group had no improvement, and some experienced a slight worsening after the sham procedure before they crossed over into the treatment group. A year following the procedure, the patients who underwent MRgFUS procedure retained a 40% improvement in these scores compared to baseline.

Another 3-year follow-up pivotal study of MRgFUS for ET sponsored by Insightec company (Pre-Market Approval (PMA) P150038) demonstrates a durable reduction in hand tremor and improvement in quality of life. (Fig. 4A)

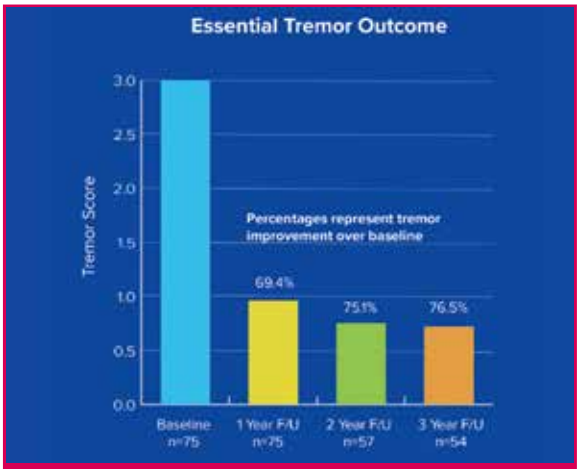

Fig. 4A: 3-year follow-up study of MRgFUS for ET demonstrates a durable reduction in hand tremor and improvement in quality of life. (Excerpted from www.insightec.com)

The most common adverse events experienced after treatment included imbalance/gait disturbance (26%), numbness/tingling (33%), and headache/head pain (51%). Most of these events were classified as mild or moderate, and 48% of all adverse events resolved on their own within 30 days. Adverse events that persisted at three years were all mild or moderate and included numbness/tingling (9%), imbalance (4%), unsteadiness (4%), gait disturbance (2%), and musculoskeletal weakness (2%). Additional infrequent events included dizziness, taste disturbance, slurred speech, fatigue and vomiting.

Results of these studies show that MRgFUS thalamotomy is safe and effective for treating essential tremor. The patients gained immediate tremor control and was able to regain ability to perform daily tasks such as eating and writing.

Other treatment options - Radiofrequency (RF) ablation, Deep Brain Stimulation (DBS) and Stereotactic Radiosurgery (SRS)

Stereotactic RF thalamotomy and DBS are additional effective methods for treating essential tremor, with RF thalamotomy resulting in tremor relief in 73–93% of patients and DBS successfully eliminating tremor in 42–90% of patients.[18,19] Tolerance to thalamic DBS has been reported in up to 30% of patients.

However, both RF thalamotomy and DBS require Burr-hole surgery and insertion of probes into the brain. These procedures may be complicated by paresthesias in 20% of the patients at 12 months, intracranial haemorrhage in 1-3% of the patients, neurologic deficits in 1-2% of the patients, and infection in 5-10% of the patients.[20,21]

SRS is also used for treatment of tremor, with studies reporting clinical improvement in 70-90% of the patients.[22,23] SRS is however limited by delayed onset of effect and does not allow immediate verification of targeting, which may limit effectiveness or result in complications, depending on the accuracy of targeting. Reported adverse effects include paresthesia, hemiparesis, speech impairment, and haemorrhage, with complication rates reported between 1.3% and 8.7%.[24]

In Hong Kong, surgical/radiosurgical treatment of medication-refractory ET has nearly never been contemplated if any, largely due to the risks involved and lack of awareness of the available treatment options. For DBS, patients in Hong Kong with ET have to purchase expensive implants as self-finance items. As such, even when the tremor is out of control by medication, the treatment pathway usually ends there. With the introduction of the safer and less invasive tMRgFUS treatment, it will be more acceptable to patients with ET in Hong Kong.

In contrary to the other surgical treatments for medication-refractory ET, MRgFUS technology:

1. provides immediate tremor improvement through an outpatient procedure,
2. has high safety profile. It carries minimal risk of infection, bleeding or other surgical complications,
3. with the help of MRI guidance, allows accurate localisation of the lesion site and real-time monitoring of the target thermal change,
4. requires no anaesthesia. As the patient is awake throughout the single-session procedure, real-time verification of treatment effect and immediate feedback of any potential side effects can be assured (by using sub-therapeutic dosing, i.e. a reduced amount of thermal energy for preliminary reversible lesioning, before doing the ultimate permanent lesioning). And
5. allows patients to quickly return to normal activity with definite symptom improvement and without need to worry about delayed side effects.

All these advantages make MRgFUS an attractive alternative to open surgery or radiation therapy for ET.

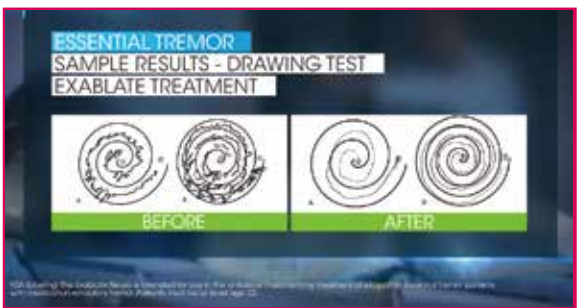

Fig. 5: Immediate testing of treatment effects (image reproduced with permission from Insightecb)

PATIENT TREATMENT JOURNEY

Potential candidates will be reviewed and discussed in regular case conference.

Patients are counselled in advance on the day of the procedure by a multidisciplinary team consisting of

the neurosurgeon, neurologist, nurse, physiotherapist, occupational therapist and clinical psychologist, if deemed suitable for the treatment.

Before the treatment day - Pre-treatment planning images including CT of the entire cranium (to calculate skull density ratio) and MRI to define the target are done. These pre-treatment MR images are registered to the treatment day MR image for delineation of the target.

On the treatment day - The patient's scalp is fully shaved, cleaned with alcohol, and examined for pre-existing scars or other lesions. An MRI-compatible stereotactic frame is affixed to the head using screws placed after injection of local anaesthesia. A circular elastic membrane with a central opening is stretched to fit tightly around the head and placed as low as possible on top of the stereotactic frame.(Fig 2A).

While the patient is being prepared, the tMRgFUS device is tested using a gel phantom to ensure proper function. The patient is then positioned supine on the MRI table entering the magnet bore.

The patient's vital signs are monitored throughout the treatment. An IV line is placed for administration of fluid or medications, in case light sedation is required at times.

Foley catheter and compression stockings (to prevent deep vein thrombosis) are recommended because of the length of the procedure. The patient's body temperature is maintained with warming blankets during the procedure. The procedure can be terminated by the patient at any time using a stop-sonication button.

Fig. 6: No anaesthesia is required throughout the procedure (Image reproduced with permission from Insightec)

The treatment planning images are used to assist -

1. precise targeting, 2.provide phase offsets, (to compensate different skull density and thickness), 3. delineate a safe sonication pathway (to avoid intracranial calcifications in the choroid plexus, falx cerebri, basal ganglia, or vessels), and 4. to demarcate no-pass regions around the sinuses and any air trapped between the elastic membrane and the scalp (because of the risk of ultrasound absorption and heating in these locations).

The amplitude of the energy from each transducer element is also modified, to result in equal acoustic intensity at the skull surface.

Fiducial markers are placed on the images along the ventricular and cortical margins to aid in movement detection.

Fig. 7: Sagittal MR images acquired before treatment and on treatment day are co-registered using CT overlay (green). Anterior and posterior commissures are marked by red cursors. (Excerpted from Ghanouni et al. Applications of Transcranial MRI-Guided Focused Ultrasound. American Journal of Roentgenology 2015; 205:150–159)

VIM NUCLEUS TARGETING

Targeting of the VIM nucleus of thalamus starts with anatomic measurement, either based on an overlaid atlas or by using measurements from an internal reference line. The VIM nucleus of the thalamus is located by measuring 6-7 mm anterior to the posterior commissure and 11 mm laterally from the edge of the third ventricle at the level of the intercommissural plane connecting the anterior and posterior commissures (Fig. 8). Final targeting is confirmed by intra-procedural neurologic examination and feedback from the awake patient.

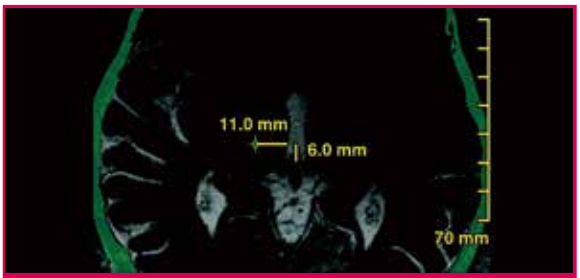

Fig. 8: The VIM nucleus of the thalamus is located by measuring 6-7 mm anterior to the posterior commissure and 11 mm laterally from the edge of the third ventricle at the level of the intercommissural plane connecting the anterior and posterior commissures (Image excerpted from Ghanouni et al. Applications of Transcranial MRI-Guided Focused Ultrasound. American Journal of Roentgenology 2015; 205:150–159)

TREATMENT STEPS

Subtherapeutic heating - Short low-energy sonications performed in the targeted area in the 40–45°C range.

Verification stage - The acoustic power is then slowly increased over several 10- to 20-second sonications, where the size and shape of the sonication spot is evaluated, with temperatures kept between 46°C and 50°C.

Clinical feedback - Further treatment to temperatures of 51–55°C may generate clinical feedback.

Thermocoagulation - by a higher temperature treatment regimen to achieve a sufficient thermal dose, targeting a 55–60°C peak temperature.

Lesion size depends on technical factors (e.g. the time after treatment and the MRI method used for measurement), but peak temperatures of 55–60°C typically produce a 4 to 5mm diameter region of ablation on T2-weighted MRI performed the day after treatment.

Both optimal coverage of the target and clinical feedback from patients play a role in determining the final peak temperatures. Patients are clinically evaluated after every sonication to assess for symptom suppression and side effects.

The total treatment time spent on the MRI table, including positioning, imaging, planning, and sonications, is usually around 3 hours.

After treatment, the patient is removed from the transducer and the stereotactic frame. The patient is then returned to the MRI table for post-treatment imaging. MR images using head coil are obtained to accurately assess the lesion's location and size.

A neurologic examination is performed after the procedure, and the patient is then monitored in the hospital for adverse events and discharged on the same day if stable.

Future Treatment - Tremor dominant Parkinson's disease (TDPD) and blood brain barrier opening (BBBO)

TDPD

In an estimated 26% of Parkinson's disease (PD) patients, the primary symptom is tremor. As the disease progresses, they may experience onset of other symptoms subsequently. However, tremor remains the symptom with the most severe impact on their daily activities.

MRgFUS provides an incisionless treatment option for patients with medication-refractory TDPD. Candidates for treatment must be Parkinsonian tremor patients 30 years or older.

In an Insightec sponsored study, median tremor scores improved 51.9% versus 12.7% for the treatment and sham groups, respectively, at 3-month follow-up (Pre-Market Approval (PMA) P150038). There was a trend of improvement from baseline observed in the treated group not seen in the sham group; such improvement persisted throughout the 12-month follow-up.

TDPD as a treatment indication in the Hospital Authority has already been submitted for approval and deliberation is in progress.

Gliomas and metastatic brain tumours

Thermal ablation of gliomas has been performed according to some case reports, with 50% to nearly all tumoral enhancement resolution. However, complications including death has been reported; such complications were postulated to be caused by the presence of cavitation within the tumour that increases the risk of haemorrhage. Recently, a patient with a metastatic brain tumour and another patient with recurrent glioblastoma successfully received limited treatment with the mid-frequency transcranial MRI-guided FUS device.[26,27]

For tumor applications, the high-frequency MRI-guided FUS system provides too small a treatment envelope because tumours are not confined to the central region of the brain. Successful application of MRI-guided FUS will require expansion of the treatment envelope through the use of low-frequency MRI-guided FUS. Ongoing work to improve cavitation detection and avoidance with the low-frequency system is underway.

In addition to thermal therapy, FUS can also be used to noninvasively and transiently disrupt the BBB.[28] Most systemically administered drugs cannot cross the BBB, which both limits transport of molecules according to their size, polarity, and hydrophilicity and also actively removes chemotherapeutic agents from the brain.[29-32]

Methods have been explored to enhance the delivery of therapeutic agents to tumours in the brain, including chemical modification of the agents so that they cross the BBB[30], intratumoral injection, convection-enhanced delivery, and combined intraarterial delivery of drugs with osmotic agents that can globally disrupt the BBB.[31,33,34]

BBB permeability is consistently enhanced through the mechanical effects of FUS on intraarterially injected microbubbles.[35,36] When exposed to ultrasound waves, the intravascular microbubbles generate mechanical forces on the vessel walls that focally open the BBB.[32,34,37,38] The ultrasound intensity needed to disrupt the BBB in the presence of microbubbles is much less than that needed for thermal ablation; thus, there is no significant heating of the skull with this approach, and no significant injury to the brain parenchyma or vasculature.[39,37,40,41]

Studies using experimental animal tumour models have shown the ability of FUS to increase the concentration of therapeutic agents in the brain. After FUS-mediated disruption of the BBB in rat brain, doxorubicin crossed into the brain parenchyma[42] and delayed the growth of implanted gliomas.[33] The antibody trastuzumab was delivered to the brain after BBB disruption in rats[36] and resulted in decreased volume of implanted ERBB2-positive breast cancer metastases and improved survival. Similar FUS-mediated methods of BBB opening have increased delivery of 1,3-bis-(2-chloroethyl)-1-nitrosourea[43] and temozolomide[44] to rat brains implanted with glioblastomas, resulting in decreased tumour size and prolonged survival.

These methods have been extended to primates, with FUS used to safely, reproducibly, and focally disrupt the BBB in rhesus macaques, potentially allowing noninvasive and repeated delivery of drugs to the human brain.[39] This may be particularly useful in the treatment of malignant glioma, which, because of its infiltration into the brain parenchyma, has not responded well to conventional treatment methods.[5,45,46] Pilot studies have also demonstrated safe reversible and repeated opening of BBB within the target volume of patients with Alzheimer's disease.[47]

As a new modality of therapeutic tools, modification and optimisation are needed for FUS-BBB opening to allow its incorporation into standard care, and properly designed clinical trials are mandatory to demonstrate its clinical benefits.

There has been significant progress in therapeutic ultrasound over the past two decades, which provides hope for CNS diseases that were previously undertreated due to hindrance by the BBB. Malignant brain tumor is at the top of the list due to its worst survival, followed by neurodegenerative diseases with a lack of efficient options for reversing the deterioration processes.

CONCLUSION

tMRgFUS provides a new treatment option for patients with essential tremor without some of the complications associated with surgery. Furthermore, tMRgFUS holds promise for a range of neurosurgical procedures and will revolutionalise all other existing treatment options.

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Rapid onset of blood pressure reduction to reach physician-specified SBP target range*† within **30 mins**[1]

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† Patients reaching SBP target range: 91.7% vs. 82.5% (with labetalol); P = 0.039.

Stabilized effect
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Well-tolerated safety profile

Fewer all-cause adverse events[3]
48% vs. 61% (with labetalol) (P = 0.04)

Lower discontinuation rate[3]
6% vs. 22% (with labetalol) (P = 0.04)

Study design[1]
The CLUE was a phase 4, multicenter, randomized, comparative effectiveness trial to determine the efficacy and safety of a premixed nicardipine infusion versus IV bolus labetalol, for management or hypertension in the emergency setting. Eligible patients were over 18 years of age, with an SBP ≥180 mmHg on two consecutive readings of 10 minutes apart. 226 patients were enrolled and randomized to receive nicardipine (110 patients) and labetalol (116 patients) respectively. The primary endpoint was the percent of subjects meeting target range of SBP within initial 30 minutes of treatment. The target range of SBP was as per the physician's discretion, based on their impression of necessity at a given clinical scenario.

Study design[2]
A single-center, retrospective, explorative analysis of individuals diagnosed with spontaneous intracerebral hemorrhage receiving labetalol, hydralazine, and/or nicardipine within 24 hours of hospital admission. Of 272 patients included, 108 patients received IV nicardipine with or without additional IV boluses (nicardipine ± labetalol and/or hydralazine), and 164 patients received IV bolus antihypertensives (labetalol and/or hydralazine) alone. Primary endpoint was blood pressure variation defined as standard deviation of SBP between treatment groups.

Study design[3]
A retrospective analysis of consecutive patients receiving intravenous labetalol or intravenous nicardipine for acute hypertension in the intensive care unit with acute elevations in either systolic (>160 mmHg) or diastolic (>90 mm Hg) blood pressure. A total of 189 patients receiving labetalol and 193 patients receiving nicardipine were included. The average hourly dose was 37.3 ± 9.4 mg/h for labetalol compared with 7.1 ± 5.6 mg/h for nicardipine (P = 0.001). The average total dose of labetalol was 170.9 ± 32.6 mg compared with 112.2 ± 29.1 mg for nicardipine (P = 0.02).

IV = intravenous. SBP = systolic blood pressure.

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Abbreviated Prescribing information
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Therapeutic indications: Intravenous nicardipine is indicated for the treatment of acute life-threatening hypertension. Particularly in the event of: malignant arterial hypertension/hypertensive encephalopathy. Aortic dissection, when short acting beta-blocker therapy is not suitable, or in combination with a beta-blocker when beta-blocking alone is not effective. Severe pre-eclampsia, when other intravenous antihypertensive agents are not recommended or are contra-indicated. Nicardipine is also indicated for the treatment of post-operative hypertension.

Posology and method of administration: Antihypertensive effect depends on the administered dose. Dosage to achieve the desired blood pressure can vary depending on the targeted blood pressure, response, and the age or general condition of the patient. Dilute to 0.1-0.2 mg/ml before use unless given via a central venous line. Adults initial dose: 3-5 mg/hr for 15 mins, increased by 0.5 or 1 mg every 15 mins. Infusion rates should not exceed 15 mg/hr. Maintenance dose: Reduce to 2-4 mg/hr when the target pressure is reached. Transition to an oral antihypertensive agent: discontinue or reduce dosage while appropriate oral therapy is established. Consider lag time before onset of effects by the oral agent. Continue blood pressure monitoring.

Contraindications: Hypersensitivity to active substance or any of the excipients listed. Severe aortic stenosis. Compensatory hypertension, in case of an arteriovenous shunt or aortic coarctation. Unstable angina, within 8 days after myocardial infarction.

List of excipients: Sorbitol, citric acid monohydrate, sodium citrate, hydrochloric acid, sodium hydroxide, water for injections.

Incompatibilities: Risk of precipitation with products in solution of pH>6 (e.g. bicarbonate solution, Ringer's solution, diazepam, furosemide, methohexital sodium, thiopental). Risk of nicardipine adsorption on the plastic materials of infusion devices with saline solutions.

Special precautions for storage: Do not store above +25°C. Store the ampoule in the outer packaging, away from light.

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Elevate Expectations

TTFIELDS

For your newly diagnosed GBM patients, their new journey is safeguarded by a start with Optune

At first GBM recurrence, keep Optune on to strive for a brighter future

From the EF-14 study,*

Doubled 5-year survival rate[1]

13% with Optune plus TMZ vs. 5% with TMZ alone (p=0.004)[1]

HRQoL maintained over time with Optune[2]

Patients reflected that addition of Optune **did not affect HRQoL** except for more itchy skin[2]

From the EF-14 study,*

Improved overall survival beyond the first recurrence on Optune plus TMZ[3]

11.8 months with the continued use of Optune plus 2L systemic treatment vs. 9.2 months with 2L systemic treatment only (HR=0.70; 95%CI: 0.48-1.00; p=0.049)[3]

Low toxicity[3]

Toxicity profile was similar in patients treated with Optune + 2L chemotherapy after first recurrence compared with patients treated with Optune + TMZ as maintenance therapy[3]

Only 13% of Optune users reported a medical device site reaction, and none was severe[3]

*__Study design of the EF-14 study__[1,2]: In the multicenter, open-label, randomized, phase 3 EF-14 study, 695 patients with newly diagnosed GBM whose tumor had been resected or biopsied and had completed concomitant radiochemotherapy were randomized 2:1 to receive Optune plus TMZ or TMZ alone. The primary endpoint was PFS, and the secondary endpoint was OS. If tumor progression occurred, second-line therapy was offered per local practice. However, in the experimental group, Optune could be continued until second radiologic progression occurred or for a maximum of 24 months. A post hoc analysis was performed to evaluate the efficacy and safety of Optune when added to second-line treatment according to physician's best choice after first disease recurrence among the patients who were enrolled in the trial.

Abbreviations: 2L, second-line; GBM, glioblastoma multiforme; HRQoL, health-related quality of life; TMZ, temozolomide; TTFields, tumor-treating fields.

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Indications for Use

Optune is intended as a treatment for adult patients (18 years of age or older) with histologically confirmed glioblastoma multiforme (GBM). **Newly diagnosed GBM** Optune (NovoTTF-200A) Treatment Kit is intended for the treatment of patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant Temozolomide, concomitant to maintenance Temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant Temozolomide. Treatment may be given together with maintenance Temozolomide (according to the prescribing information in the Temozolomide package insert) and after maintenance Temozolomide is stopped. **Recurrent GBM** Optune (NovoTTF-200A) Treatment Kit is intended for the treatment of patients with recurrent GBM who have progressed after surgery, radiotherapy and Temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy or chemotherapy. **Contraindications** *The directions below are written in the language directed to the patient.* Do not use Optune Treatment Kit if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Treatment Kit was not tested in pregnant women. Do not use Optune Treatment Kit if you have significant additional neurological disease (primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus associated with increased intracranial pressure). Do not use Optune Treatment Kit if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Treatment Kit may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure. Do not use Optune if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers and defibrillators. Use of Optune together with implanted electronic devices has not been tested and may lead to malfunctioning of the implanted device. Use of Optune together with skull defects or bullet fragments has not been tested and may possibly lead to tissue damage or render Optune ineffective. Ref: Commercial Optune Physician Instructions For Use Version 1.1, Document number QSD-QR-711 EN(HK), Release date: Dec 2020.

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Novel Treatment for Glioblastoma - Tumour Treating Fields, the Fourth Modality in Oncological Treatment

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GLIOBLASTOMA MULTIFORME (GBM)

Primary brain tumour is uncommon in adults and glioma accounts for the majority. Most of the gliomas diagnosed are glioblastoma multiforme (GBM), which is the most malignant form of glioma and is classified as WHO (World Health Organization) grade 4 brain tumour. There are approximately 70 new patients every year in Hong Kong[1]. Unlike most solid tumours that have a discrete border between tumour and surrounding healthy tissue, GBM is a diffuse glioma without distinct borders, which renders complete surgical excisionimpossible (Fig. 1). Even so, the mainstay of treatment remains to be maximal surgical resection for cytoreduction if technically feasible, followed by Stupp regimen consisting of a combination of radiotherapy and chemotherapy[2].

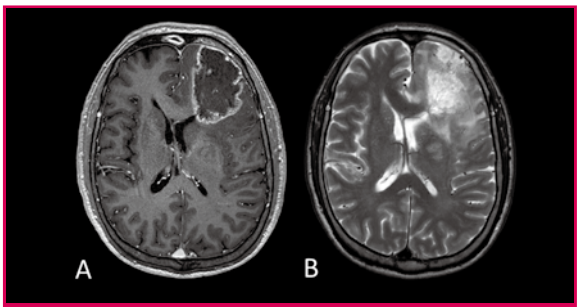

Fig. 1. (A) MRI T1-weighted axial image of a 64 years old man presented with 2 months history of cognitive decline showing a gadolinium enhanced tumour at left frontal lobe causing subfalcine herniation with hypointense signal at the centre represents necrotic area due to the rapid growth of GBM. (B) MRI T2-weighted axial image showing hyperintense signal beyond the gadolinium enhancing margin with infiltrating tumour of lower tumour cellular intensity and vasogenic edema. (Clinical photos from personal collection)

Stupp regimen has been the standard of care for newly diagnosed GBM since 2005. The regimen starts with concomitant radiotherapy at 60Gy in 30 fractions and oral chemotherapy using temozolomide (TMZ) to be completed in six weeks. It is followed by six cycles of adjuvant chemotherapy with TMZ for five consecutive days in each 28-day cycle[2]. In spite of the fact that this regimen can significantly boost up both progression-free survival (PFS) and overall survival (OS) to 6.9 months and 14.6 months respectively, GBM remains a disease of grave prognosis. Furthermore, there is no standard treatment for recurrent GBM. Even though bevacizumab has been approved by the U.S. FDA for recurrent glioblastoma, bevacizumab prolongs PFS but not the OS, which renders this drug not universally accepted by certain authorities such as The National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC)[3]. There has been no breakthrough in GBM treatment until 2012 and 2015 when two respective phase III trials showed Tumour Treating Fields (TTF), a new treatment modality, is effective for both recurrent and newly diagnosed GBM[4,5].

TUMOUR TREATING FIELDS

It was almost two decades ago when Kirson et al. reported intermediate frequency (100-300kHz) alternating electric fields prolonged tumours cell mitosis and destroyed mitotic tumour cells, while normal cells were unaffected in vitro[6]. The mechanism underlying this technology is that many intracellular molecules such as tubulins, which are essential for cell proliferation, are dipolar and their orientation can be affected by the external electric field. When non-uniform electric fields are applied, these dipolar molecules will move towards high-intensity field. During the metaphase of the cell cycle, molecules such as tubulins will polymerise to form microtubules, and other organelles will migrate to the two poles of the dividing cells. External application of alternating electric fields disrupts these processes in the cell cycle such that cell division cannot take place, resulting in abnormal chromosomal segregation and cell death (Fig. 2)[6-8]. This immediate frequency alternating electric fields have since been renamed as Tumour Treating Fields (TTF). The frequency is tumour-specific; TTF at 200 kHz are most effective on glioma cells[9]. In an in-vitro study, TTF increased human glioma sensitivity to TMZ[10]. Following this study, ten patients with recurrent GBM and another ten patients with newly diagnosed GBM were both treated with TTF alone as salvage therapy and in parallel to maintenance TMZ respectively[9,10]. The result was encouraging as there was a major leap in both OS and PFS, in both recurrent and newly diagnosed GBM patients, which was a breakthrough since the 2005 Stupp regimen.

NOVEL TREATMENT FOR GBM

The results from the pilot study served as the basis for the later EF-11 study, which is a phase III trial comparing TTF as monotherapy to the best chemotherapy according to the physician's best choice[5]. Two hundred and thirty-seven patients recruited from September 2006 through May 2009 were randomised in 1:1 ratio, at a median use of 20.6 hours per day. The median OS was 6.6 months and 6.0 months (p = 0.27),

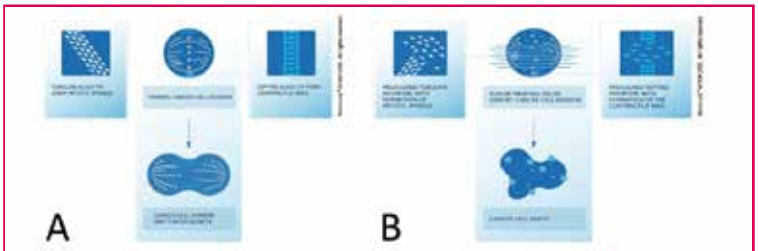

Fig. 2. (A) Usual healthy and tumour cells proliferation. (B) Abnormal tumours cell proliferation affected by TTF. (Reproduced with permission from © 2021 Novocure GmbH – all rights reserved.)

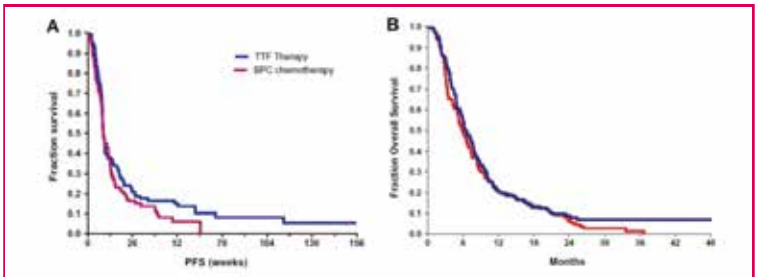

Fig. 3: Results from EF-11. (A) Progression free survival. (B) Overall survival. Kaplan-Meier curves (Reproduced with permission from Stupp R, Wong ET, Kanner AA, et al., 2012 5). BPC: Physician's Best Choice.

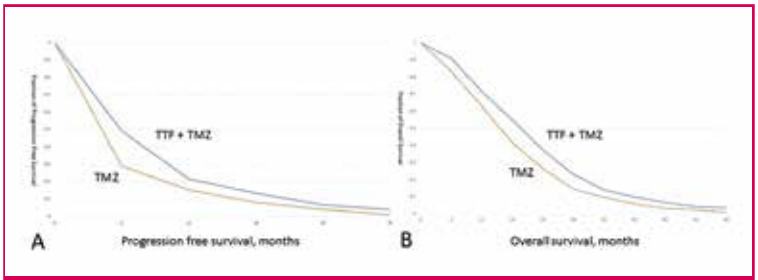

Fig. 4: Results from EF-14. (A) Progression free survival. (B) Overall survival. Kaplan-Meier curves[13]. (Adapted from Stupp R, Taillibert S, Kanner A, et al.)

median PFS was 2.2 months and 2.1 months (p = 0.16), for TTF and chemotherapy groups, respectively (Fig. 3)[5]. While this study was designed for superiority, the absence of significant difference suggested TTF was at least comparable to chemotherapy if not better. At the same time, TTF group experienced fewer systemic side effects apart from mild to moderate scalp contact dermatitis that could be easily treated with topical steroids. Subsequent post-hoc analysis showed a significant difference in median OS of 4.5 months and 7.7 months when patients' monthly compliance with TTF was < 75% and >=75% respectively[11]. The importance of treatment compliance on OS was further supplemented by a review on Patient Registry Dataset (PRiDe) on 457 recurrent GBM patients who received TTF in the US commercial prescription-use programme between October 2011 and November 2013[12]. The PRiDe reflects more of the real-world experience where patients were not restricted to the number or types of prior treatment. Apart from confirming that daily compliance >=75% had significantly longer median OS than those with lesser compliance, this review also reported a longer median OS of 9.6 months compared to 6.6 months reported in EF-11. Therefore, for recurrent GBM patients who cannot tolerate chemotherapy, TTF is a comparable alternative and,as part of combination therapy, may provide additional survival period.

Immediately after completion of EF-11 study, 695 newly diagnosed GBM patients were recruited in the EF-14 study which was started in Jul, 2009. This trial is an open-label, randomised phase 3 trial to study the effect of adding TTF as part of adjuvant treatment in Stupp regime[4]. Patients were randomised at a ratio of 2 to 1 with 466 and 229 patients using TMZ + TTF and TMZ alone respectively. The study was terminated in Nov, 2014 as an interim study having a median follow-up of 38 months showed a median PFS of 7.1 months and 4.0 months in TTF + TMZ and TMZ alone patients respectively (p = 0.001)[4]. In addition, median OS was 20.5 months with the addition of TTF compared to 15.6 months in those without (p=0.004). The increment in both PFS and OS supported U.S. FDA to approve the use of TTF in newly diagnosed GBM patients. The final study result was published two years later and had a median follow up of 44 months[13]. With a median treatment duration of 8.2 months, the median PFS was 6.7 months and 4.0 months; medial survival was 20.9 months and 16.0 months, for TTF + TMZ and TMZ alone respectively (Fig. 4). Like recurrent GBM patients,

in newly diagnosed GBM patients, daily usage of 18 hours or more (i.e. >= 75%) is associated with significant longer OS than those with usage less than 18 hours (22.6 months vs 19.1 months, p=0.009). Patients with TTF also had a longer time to a sustained 6-point decline in the Mini-mental State Examination score and a sustained 10-point decline in Karnofsky performance scale. In another study on health-related quality of life (HRQoL) of the same group of patients, in line with the findings in EF-14, the addition of TTF resulted in significant longer deterioration free survival in global health status, physical and emotional functional, pain, and weakness of leg[14]. The oncological effect of TTF after first tumour recurrence was reported in the post hoc analysis of EF-14 patients where those with TTF plus chemotherapy had a median OS of 11.8 months compared to 9.2 months in patients with chemotherapy only (p=0.049)[15]. In terms of safety, the EF-14 study showed the addition of TTF did not increase systemic treatment toxicity apart from skin toxicity[13]. This was confirmed by global post-marketing safety surveillance of 11,029 patients with reported prevalence of skin reaction of 34%[16].

OBSTACLE TO THE NEW TREATMENT

While the results were encouraging, the adoption of this new treatment modality is slow because of the high cost in return for a limited gain in survival time. The official price, including Hong Kong, is USD$20,000 per month, for renting hardware, consumables like transducer arrays and supporting services. A cost-effectiveness analysis of TTF in newly diagnosed GBM patients reported the calculated cost was €292,353 per life-years gain, assuming a life-expectancy of 22.08 months with TTF and 18 months without TTF, when the cost of TTF was €10,000 per months[17]. The result from another similar study fared little better at USD$150,452 per life-years gain[18]. Therefore, TTF is yet to be financially supported by national health authorities widely including in Asia. While Korea is the first place in Asia having the initial experience on TTF when taking part in the EF-14 study, TTF was first clinically available in Asia when it landed in Japan in 2015 followed by Hong Kong by the end of 2018. The clinical trial result and post-marketing safety result were reported from 24 Korean patients and 153 Japanese patients respectively[16]. In Hong Kong, only limited number of patients had received the treatment, mainly in the private sector and by civil servants in public hospitals. Clinical data from them is limited at the time of writing and yet to be certain if it is comparable to study results.

HOW TO APPLY

TTF is applied through two pairs of transducer arrays over the head that are connected to the electric field generator (Fig. 5). The generator is portable and requires battery change every several hours to maintain continuous treatment. The arrangement of the arrays is planned by the treating physician using a designated planning software to contour the tumour on patient's MRI image, such that the field is more concentrated on the tumour to maximise the treatment effect. The most common side effect of TTF is skin allergy over the scalp to medical adhesives and conductive hydrogels that respond to hydrocortisone cream most of the time (Fig. 6A, 6B). A dedicated caretaker is needed to examine the scalp, helps the patient to maintain scalp hygiene, shave the hair, apply new arrays every two to three days, as well as to maintain the power supply for the generator (Fig. 6C). This caretaker is essential to maintain patient's treatment compliance and so the effectiveness, as many GBM patients have cognitive deficit upon presentation, after surgery and radiotherapy.

Fig. 5: (A) TTF hardware, transducer arrays, electric field generator, battery, charger. (Reused with permission from © 2021 Novocure GmbH – all rights reserved.) (B) A local patient with transducer arrays and electric field generator having treatment. (Clinical photo with patient's permission)

Fig. 6: (A) Skin allergy two weeks after TTF. (B) Six weeks after TTF, scalp back to normal after applying hydrocortisone cream without interrupting TTF treatment. (C) Patient's wife applying new transducer arrays to patient. (Clinical photos with patient's permission)

STRENGTH AND WEAKNESS

With surgery, medical therapy and radiotherapy (RT) being the mainstay of oncological treatment, TTF becomes the fourth modality. To a certain extent, TTFresembles external RT, utilising energy from the outside and concentrating that energy on the tumour. Unlike RT, the tumour cell-specificity behaves like targeted therapy inducing no harm to the surrounding

tissues. Without worrying about radiation toxicity even at large planning target volume, TTF can be applied to large tumours if the transducer arrays can generate a field of sufficient volume. The inherent nature of TTF in lacking a rapid falloff of the fields also produces treatment effect, where indicated, on nearby tissue that may harbour micro-metastases, which is translated into a much bigger clinical target volume than gross tumour volume. It seems to be an ideal oncological treatment: non-invasive, easy to apply, tumour targeted with no or minimal effect to healthy tissue, mild and transient side effects.But because of the electric fields, medical conditions such as epilepsy, or presence of active medical implants such as pacemaker, defibrillator, deep brain stimulator, programmable valve for ventriculoperitoneal shunt, are contraindications. Furthermore, TTF requires good patient compliance, as it demands long treatment duration, during which the patient must bear with the hardware, until there is evidence of treatment failure.

THE FUTURE OF TTF

Apart from GBM, TTF has also been approved by the US FDA for treating recurrent malignant pleural mesothelioma after STELLAR trial (Fig. 7A)[19]. More trials are ongoing for cerebral metastatic non-small cell lung cancer (NSLC), and extracranial diseases including advanced stage NSLC, pancreatic ductal adenocarcinoma, ovarian cancer, hepatocellular carcinoma and gastric cancer, using different frequencies to target tumour cells while sparing normal tissue (Fig. 7B) [7, 19-21].

Along with the accumulating results and experience, the indication of TTF is expanding and no doubt this novel modality will come in different combinations of radiotherapy and drug for tumour treatment. This is the usual path of all new treatments to gain popularity followed by price reduction.

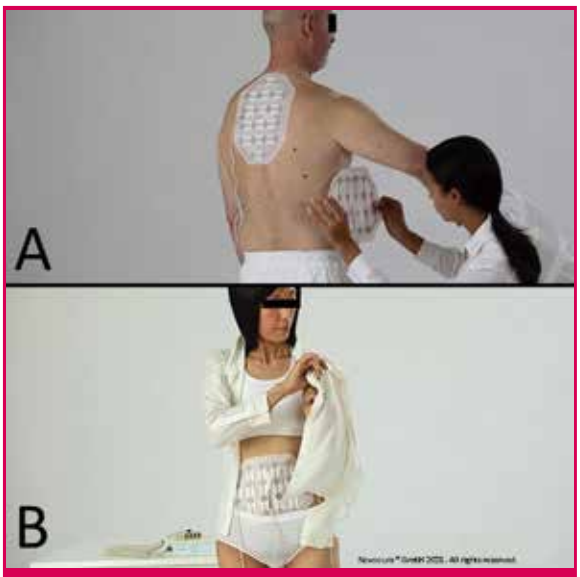

Fig. 7: (A) Transducer arrays applied to chest for mesothelioma and carcinoma of lung. (B) Transducer arrays applied to abdomen for ovarian carcinoma. (Reproduced with permission from © 2021 Novocure GmbH – all rights reserved.)

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Smart Neurosurgical Operating Room in the New 5G Era

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INTRODUCTION

With the emergence of new technologies, the surgical working environment becomes increasingly complex and comprises many medical devices for seamless integration to achieve maximal efficiency. The concept of Digital Operating Room (OR) or Smart OR has been evolving and implemented in the United States since more than 20 years ago[1,2]. Smart OR functions as a central hub for clinical image data integration inside the OR and serves to record, collect and forward data to the hospital information technology (IT) system. Via the central console, the system can functionally connect the whole OR environment and control specified display data and images from various neurosurgical operating devices. Besides the connectivity in OR, centres are also finding ways to reduce OR turnover time and increase caseload in order to increase the surgical efficiency[3]. The Smart OR is designed to transform surgery from an analogue process, where standalone equipment are not inter-connected, into a digital process where data are shared. It can support surgical teams by providing them with a rich stream of data from networked medical tools as well as AI-powered advice on surgical options in the background of "smart hospital" (Fig. 1).

UNIQUENESS IN NEUROSURGERY

Neurosurgery itself is always a perfect match with advanced technology as it is an inherently technical field. Modern neurosurgery consists of the integration of intraoperative imaging, precise neuro-navigation, surgical planning tools and software, robotic system, state-of-the-art surgical microscopes and endoscopes with 4K and 3D visualisation, heads-up displays, virtual reality (VR) and augmented reality (AR)[4,5,6]. The rapid advancement in technology, particularly related to intraoperative neuro-navigation systems and imaging modalities, e.g. Magnetic Resonance Imaging (MRI), Computerised Tomography (CT), Digital Subtraction Imaging (DSA), Ultrasound (USG), improves patient care and perioperative safety of neurosurgical patients. Cheary et al. in 2002 already published the concept of technology development of an integrated system to enable the next generation of percutaneous spine procedures[7]. This is particularly advantages in operating on unconscious patients who cannot be mentally engaged in surgical time-out procedures. We always treat diseases at microscopic level that requires precise imaging processing and analysis. This evolving digital technology application is not limited to the operating room only, but extends to surgical planning and discussion, patient education and consultations (Fig. 2). Meyer et al. from MGH in 2007 presented their prototype system to perform integration and display of information from a variety of disparate sources, which include hospital information systems, patient monitors, surgical equipment and a location tracking system[8], and the application of automatic identification technologies in OR[9].

Fig. 1: Example of Smart OR system as a central hub (Reused with permission from Brainlab)

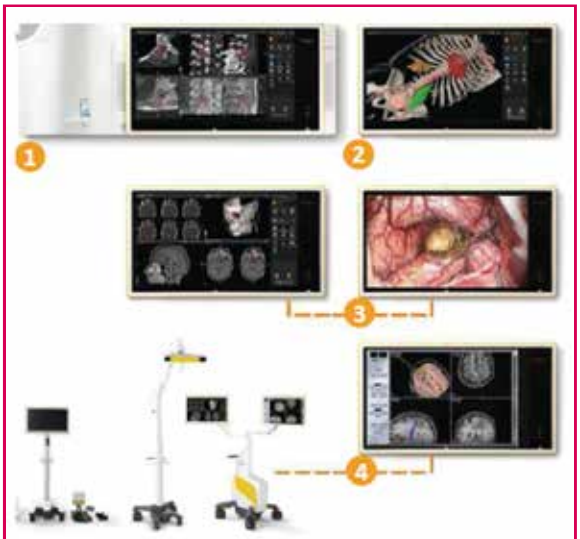

Fig. 2: Smart OR system with panels showing various information required (Reused with permission from Brainlab)

SOLUTION TO CURRENT MEDICAL SYSTEM

We have been facing the increasing challenge in the current medical health system particularly in public health service for years. There is relentless rise in patient attendance and an increase in annual operating cases with climbing waiting times for operations. Shortage of manpower and tight scheduled operation sessions are another concerned areas. Incompatibility and connectivity problems of equipment and systems in OR results in fragmented communication in both between OR and OR, and OR and other areas in the hospital, of which human error is another key area of concern. To reduce human contributing factor in OR, Spring et al. used their computerised system called "Anaesthesia Billing Alert System (ABAS)" to improve the median time in correcting documentation errors from 33 days to 3 days[10].

In the COVID-19 pandemic, our healthcare system colleagues have adopted the so-called "new normal" measures in terms of the development of new protocols, rescheduling of elective operation lists in response to the pandemic status, and implementation of virtual communication between medical colleagues and patients. Better preoperative planning with a planning system can minimise patient contact time and maximise the OR time usage. Minimal travel and in-person meetings between various medical centres promote the application of video streaming and conferencing. The system with tele-care function can increase remote patient engagement and boundless bi-directional interaction and monitoring.

ADVANTAGES OF DIGITALISATION IN OR

The key functions of smart OR include integration of medical devices, documentation, and DICOM enrichment in planning and communication (Fig. 3). The central equipment collects large amounts of complex data, clinical guidance and protocol, current interventional practices, caregiver skillset, and patient preferences. Real-time tracking is possible for all the surgical procedures, actions performed, events happened, and the current patient clinical status during the operation[12]. The beauty of protocol-driven surgical workflows in digitalised OR systems can enable automation in daily work practice and smart patient journey. Simplicity in workflow and data transfer and processing, and the integrated interface of the OR system, can match the existing and future intraoperative medical devices from different vendors. The power in using touchless control by using speech, gesture recognition, eye tracking, etc. facilitates the operating team to have seamless handling of the OR environment, image display and video recording (Fig. 4). Guerlain et al. used their OR system to perform analysis of performance measures such as technical judgements, team performance, communication patterns and human performances[13]. These advantages serve as tools to achieve the following digital value generation objectives:

1. Increase surgical efficiency
2. Minimise patient data error
3. Improve cost-effectiveness
4. Enhance multi-disciplinary teamwork partnership
5. Improve patient journey
6. Encourage training and education
7. Align with smart hospital development direction

Fig. 3: Key functions of smart OR system (Reused with permission from Brainlab)

Miehle et al. in Germany has developed the concept of intelligent digital assistance for clinical ORs (IDACO) by application of voice interaction systems. The main functions of the system include: 1. Provide data about surgery, 2. Save preferred device settings and transmit parameters of devices, 3. Control surgical devices automatically, 4. Track the usage of surgical materials and 5. Allow emergency mode for unforeseen incidents during a procedure[14].

Fig. 4: Smart OR system can allow display of information in different connected areas and the image display can be manipulated by the operating surgeon using mobile device (Reused with permission from Brainlab)

CONSIDERING FACTORS IN SMART OR SETUP

Apart from the hardware equipment required, workflows in pre-operative, intra-operative and post-operative phases should be in good organisation in order to reach success. Documet et al. listed their experience in introduction of a multimedia electronic patient record as follows.[15]

1. Lack of standards from peripheral data and imaging devices used in the OR;
2. The clinical environment was different from the laboratory environment;
3. The clinical institution was not always in control of its computer and IT equipment;
4. User acceptance; and
5. Graphical user interface appeared challenging for new users.

Another paper from Germany stated the potential exogenous and endogenous challenges and dilemmas in the hospital when deciding on digital or smart solution[16]:

1. Strategic challenges
2. Infrastructural IT problems
3. Economic trade-offs
4. Security issues
5. People constraints
6. Organisational concerns

SMART OR WITH 5G

The functions of Smart OR with digitalisation system can certainly be escalated to a higher level along with the implementation of 5G mobile technology. This new technology provides ultra-high-speed and low-latency mobile radio communication, and supports massive storage and processing of clinical images. Its capacity to send large volumes of data at high speed allows live uninterrupted retransmissions, and therefore zero-latency video streaming is possible. Doctors can monitor and supervise operations remotely and offer real time consultation support and advice to surgeons who are physically carrying out the operation. This tele-mentored live surgery can be applied in intra-hospital, inter-hospital, remote location and mobile location manners. 5G infrastructure can resolve the hurdle to effective teaching by enabling surgeons in the operating room to teach a large group of medical trainees in a separate conference room with bi-directional interaction. In addition, the implementation of neurosurgical robotic system together with 5G mobile technology will facilitate the development of tele-surgery in neurosurgical field[17,18,19].

One case illustration is a patient suffering from Parkinson's Disease who received China's first 5G-based remote surgery with a deep brain stimulation (DBS) surgery in 2019. The surgery was performed by Professor Ling Zhipei, chief physician of the First Medical Center of the Chinese PLA General Hospital (PLAGH) in Beijing. He manipulated the surgical instrument in Beijing while the patient underwent the surgery in Sanya City, Hainan, 3,000 kilometres away from Beijing. The whole DBS surgery lasted for about 3 hours and was uneventful (Fig. 5).

Fig. 5: First Tele-surgery performed in China with the support of 5G mobile technology (Reused with permission from Brainlab)

Fig. 6: The first trial of 5G-enabled smart OR system in QEH with real-time connection and communication between operation theatre and conference room (Reused with permission from Brainlab)

In Hong Kong, the Department of Neurosurgery at Queen Elizabeth Hospital (QEH) undertook the

implementation of 5G-connected neurosurgical operating room in December 2021. The first trial operation using 5G-enabled Digital OR system was an awake craniotomy for epilepsy surgery after stereoEEG (SEEG) implantation in 2021. Our neurosurgical operation theatre was connected to a conference room with real-time bidirectional interaction between two sides (Fig 6). The patient had excellent performance in the whole awake surgery with direct interaction with the teams in operation theatre and conference room. The surgery finished in expected time length and he had uneventful recovery with no breakthrough seizure after the surgery.

CONCLUSION

Neurosurgery in the era of digitalisation and 5G connectivity promises to take better surgical outcome and speedy patient recovery to the next level. Advanced technology is expected to assist the surgical team to have seamless communication, and thorough planning and preparation for successful operations.

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Lovebird
Love • Bird

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Dr Rebecca YT NG

To have lovebirds as pets had been my dream during my young adulthood.

My first experience with pet birds dated back to my secondary school years, when one day my dad came home with two of them. I was deeply attracted by the little vivid rainbow-coloured creatures and it was love at first sight.

There was no internet then and so it was not easy to find information on how to raise them properly. Ironically, without much knowledge, things became easier. The daily routines were: cleaning their cage basin; feeding them with only seeds which were available at $10 per bag in the bird market and good for the whole month; changing the water in the water dish. It took me less than 10 minutes every day.

Nowadays things have become more sophisticated. It is similar to raising kids in that you would like to offer the best food, drink and living environment to them. This is particularly true when there are eight birds. The same routine now takes more than an hour each day because of the increased food varieties and more attention required. Yet the enjoyment that they bring in return is tremendous.

Here are some of the myths and facts about lovebirds:

WHY ARE THEY CALLED LOVEBIRDS?

The genus name of lovebird is 'Agapornis'. It is literally translated into ''lovebird''. The Greek word 'agape' means 'love' and 'ornis' means 'bird'. Despite their small body size, they are parrots. They are so named because of their strong pair bonding. A pair of lovebirds will often bond strongly with each other even if they are of the same sex.

WHAT ARE THE DIFFERENT TYPES OF LOVEBIRDS AND WHERE DO THEY ORIGINATE FROM?

There are nine species of lovebirds, though only a few are typically available as pets, namely peach-faced, masked and Fischer's. Most lovebird species are native to the continent of Africa. Their size ranges from 5 to 6.6 inches, and they have short blunt tail features and stockier bodies. All these make them look cute, thus becoming popular pets.

As curious and inquisitive creatures, they always want to explore the environment. (Personal collection)

Living Room : the television is one of their favourite resting place. (Personal collection)

WHAT ARE LOVEBIRDS' CHARACTERISTICS?

Some people describe the lovebird as a 'big parrot in a small body'. They might be small, but they are bold, inquisitive, curious and always on the go. A single lovebird needs plenty of social interaction with people in his/her life, as well as plenty of busy work in the form of chewing up and destroying toys and safe items.

While they are no doubt very lively, they might not be as loving as they seem to be. A female lovebird can become highly defensive of her territory, i.e. cage, and exceedingly hostile when they are hormonal. I always have the feeling that they are a 'dinosaur inside a bird's body. Besides having different characters between individual lovebirds, they also demonstrate emotions like happiness, depression, excitement, and amazingly even jealousy.

DO THEY TALK?

Not all parrots talk. Lovebirds are well-known for their little talking ability in the human language but they are a chatty bunch, singing, whistling and talking to each other all day long and can be very noisy.

HOW LONG DO THEY LIVE?

With proper care and a well-balanced diet, a lovebird can live for 12 to 15 years or more. In forums, some lovebird owners claim that their little pets live up to 22 to 23 years.

CAN I DIFFERENTIATE BETWEEN A MALE AND FEMALE LOVEBIRD JUST BY THEIR PHENOTYPE?

They are not sexually dimorphic. There is a slight difference in their body build or behaviour but these cannot be reliably used to differentiate the gender. As an example, two of my bonded female lovebirds demonstrate mating behaviour so behaviour is unreliable.

Some of the breeders or owners of stalls at bird markets claim they can differentiate the gender of a lovebird by palpating their pelvic bone but it is again not reliable. The only reliable way is by doing blood tests and having their DNA tested. Another much more invasive way is to do surgical sexing.

WHAT SHOULD I FEED THEM?

In the wild, lovebirds live in small flocks and are granivores and frugivores.

They eat fruits, vegetables, grasses as well as seeds. For lovebirds in captivity, diet is even more important because most of the diseases in pet lovebirds are diet-related such as fatty liver or vitamin-A deficiency. A seed-only diet can result in malnutrition as seeds are usually high in fat content while lacking certain nutrients or minerals. Advice from the veterinarian would be feeding high quality pellets which are a formulated diet preferably made from organic grains and plants. It provides the birds with essential nutrients and does not afford them the choice to pick through and eat only the bits they like. Popular brands include Harrison's Bird Foods and Lafeber. Ideally, pellets should represent 75 - 80% of their diet. Variety is also very important for birds so vegetables and fruits should be provided to supplement the pellet, ideally constituting around 25% of their diet. Seeds and nuts should be provided in small portions.

Junk food such as chocolate, caffeinated food and alcohol should be avoided. Avocados have been reported to be potentially toxic and should be avoided. Fresh water should always be available. Water dishes should be cleaned daily.

HOW SHOULD I CARE FOR THEM?

Lovebirds are inquisitive and seemingly always on the go. We should offer the biggest cage that is affordable by the owner. It will be ideal if perches made of real tree branches with tree bark are provided. Perches with sandpaper are generally abrasive for the bird's feet so it should be avoided. I also offer small huts for my birds as a safe place to rest and hide.

Toys are crucial to properly engage lovebirds. Parrots are highly intelligent animals. Wild lovebirds spend most of their time foraging (finding food) but captive birds do not have to do so. Lack of stimulation potentially results in behavioural problems and self-mutilation.

Same as human, the more exercise lovebirds get, the better for their health. Time out of the cage is important as flying gives them vigorous exercise. Flight promotes longevity as well as mental well-being. Because of their intelligence, they also need a lot of attention. Out-of-cage activities provide plenty of stimulation to them besides physical exercise. However, safety is of utmost importance during their out-of-cage time. They should always be supervised.

When the babies were young, the colour of their feather was not as bright as adults. (Personal collection)

Care should be taken to make sure all the doors and windows have been closed as they are excellent escape artists. Other safety measures also need to be considered including limiting access to the stove, turning fans, big water container such as the toilet bowl and the sink with water, and iron or any electric appliance that is hot or may release toxic gases. For example, fumes releasing from the non-sticky surface of pan made from polytetrafluoroethylene (PTFE) is known to be toxic. Along the same lines, one point that cannot be overlooked about safety precautions is to watch out for birds before closing any doors and sitting on any chair or sofa as accidents do happen. They can be switching spots without anybody noticing as they are small and agile.

Toys such as swing are their all-time favourite. (Personal collection)

They always preen their partners as an action of love. (Personal collection)

Lovebirds can be perfect and loving pets but taking care of these amazing little creatures takes a lot of devotion, time and effort. One has to give up the idea of having a clean and quiet home as they can be really noisy and messy. That being said, the joy and love brought by them are irreplaceable. They also help to relieve my stress after a long day as a neurosurgeon.

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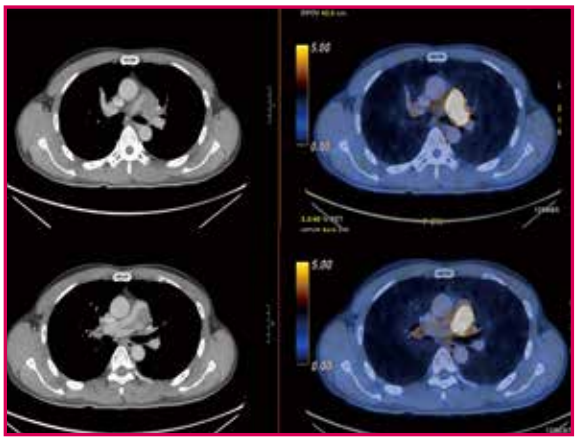
- http://lafeber.com/pet-birds/birds-live-long/?utm_source=ActiveCampaign&utm_medium=email&utm_content=Why%20Parrots%20Live%20So%20Long&utm_campaign=Pet%20Birds%20newsletter%20-%20week%20of%208%20November%202018
Why Birds Live So Long (Posted on November 14, 2013 by Susan Orosz, PhD, DVM, Dipl ABVP (Avian), Dipl ECZM (Avian))

Radiology Quiz

Dr Kelvin KH CHOI

MBChB, FRCR (UK)

Dr Kelvin KH CHOI



Questions

1. What is the abnormality?
2. What is the likely diagnosis?
3. What is the next investigation to undertake?

(See P.41 for answers)

Medical Diary of April

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	★Zoom Live Recent Updates On The Management Of Rheumatoid Arthritis - Online 4	5	6	★Zoom Live Latest Data on Meningococcal Disease and Prevention with Real World Evidence 7	8	9
10	★Zoom Live Acute Watery Diarrhea In Children - Online 11	★Zoom Live HKMA-HKSH CME Programme 2021-2022 (Physical Lecture + Online) 12	★The Hong Kong Neurosurgical Society Monthly Academic Meeting -To be confirmed 13	★Zoom Live HKMA-HKSTP CME Lecture - The Use Of C-Peptide And Other Biogenetic Markers In The Assessment Of Patients With Diabetes (Online) 14	15	16
17	18	19	★Zoom Live Management of Paediatric Asthma 20	★Professorial Webinar Management of diabetic kidney disease in 2022: what's hot? 21	★Zoom Live Latest Advancement in Clinical Data: SGLT2 Inhibitors in Heart Failure - Online 22	23
24	25	★Zoom Live HKMA-GHK CME Programme 2021 - 2022 - Update on Dementia and Mild Cognitive Impairment (Online) 26	27	★Zoom Live Updates in Management for IPF - Online 28	★Zoom Live Low Back Pain & Sciatica 29	30

Date / Time	Function	Enquiry / Remarks
4 MON 2:00 PM	**Zoom Live** **Recent Updates On The Management Of Rheumatoid Arthritis - Online** Organiser: Hong Kong Medical Association Speaker: Dr Wong Ching-han, Priscilla	HKMA CME Dept. 3108 2507 1 CME Point
7 THU 2:00 PM	**Zoom Live** **Latest Data on Meningococcal Disease and Prevention with Real World Evidence** Organiser: HKMA-Hong Kong East Community Network Speaker: Dr LAU Shing-chi	Ms Candice Tong 3108 2513 1 CME Point
11 MON 2:00 PM	**Zoom Live** **Acute Watery Diarrhea In Children - Online** Organiser: Hong Kong Medical Association Speaker: Dr LAM, Jenks Albinus	HKMA CME Dept. 3108 2507 1 CME Point
12 TUE 2:00 PM	**Zoom Live** **Recent Updates On The Management Of Rheumatoid Arthritis - Online** Organiser: Hong Kong Medical Association Speaker: Dr Wong Ching-han, Priscilla	HKMA CME Dept. 3108 2507 1CME Point
13 WED 7:30 AM	**The Hong Kong Neurosurgical Society Monthly Academic Meeting -To be confirmed** Organiser: Hong Kong Neurosurgical Society Speaker: Dr CHEUNG Ling-kit	Dr Calvin MAK 2595 6456 1.5 CME Point
14 THU 2:00 PM	**Zoom Live** **HKMA-HKSTP CME Lecture - The Use Of C-Peptide And Other Biogenetic Markers In The Assessment Of Patients With Diabetes (Online)** Organiser: Hong Kong Medical Association & Hong Kong Science Park Speaker: Prof LUK On-yan, Andrea	HKMA CME Dept 3108 2507 1CME Point
20 WED 2:00 PM	**Zoom Live** **Management of Paediatric Asthma** Organiser: HKMA-Hong Kong Central, Western & Southern Community Network Speaker: Dr SIT Sou-chi	Mr Jeffrey Cheung 2527 8285 1CME Point
21 THU 7:30 PM	**Professorial Webinar** **Management of diabetic kidney disease in 2022: what's hot?** Organiser: Hong Kong Chinese Medical Association Ltd. Speaker: Prof. Sydney Chi-wai TANG	HKCMA Ms Stone Tse / Ms Candy Lam Tel:2821 3519 1CME Point
22 FRI 2:00 PM	**Zoom Live** **Latest Advancement in Clinical Data: SGLT2 Inhibitors in Heart Failure - Online** Organiser: HKMA-KLN City Community Network Speaker: Dr CHAN Ki-wan	Ms Candice Tong 3108 2513 1CME Point
26 TUE 2:00 PM	**Zoom Live** **HKMA-GHK CME Programme 2021 - 2022 - Update on Dementia and Mild Cognitive Impairment (Online)** Organiser: Hong Kong Medical Association & Gleneagles Hong Kong Hospital Speaker: Dr Chu Yim-pui, Jonathan	HKMA CME Dept 3108 2507 1CME Point
28 THU 2:00 PM	**Zoom Live** **Updates in Management for IPF - Online** Organiser: HKMA-New Territories West Community Network Speaker: Dr Wan Chi-kin	Mr Jeffrey Cheung 2527 8285 1CME Point
29 FRI 2:00 PM	**Zoom Live** **Low Back Pain & Sciatica** Organiser: HKMA-Shatin Community Network Speaker: Dr WONG Wah-bong	Ms Candice Tong 3108 2513 1CME Point

Answers to Radiology Quiz

Answers:

1. CTPA (left) showed a large filling defect in the left pulmonary artery; PET-CT (right) confirmed these filling defects are metabolically active.

2. The presence of hypermetabolic activity discourages the diagnosis of bland thrombus which is the commonest cause of pulmonary artery filling defect. The main differential diagnosis in this case includes malignancy of vascular origin or infected / tumour thrombus.

3. Histological confirmation is required to guide further management, and extensive surgical resection will be needed if malignancy is confirmed. Upon endovascular sampling, the diagnosis is confirmed to be high-grade sarcoma. The patient subsequently underwent endarterectomy of thoracic vessels.

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- After surgery, in those patients who are unable to be fed via the enteral route, and in whom total or near total parenteral nutrition is required, a full range of vitamins and trace elements should be supplemented on a daily basis[3]

Approved for children ≥ 2 years

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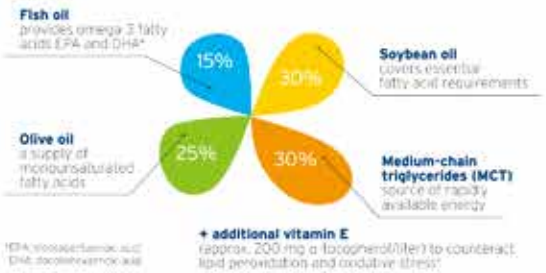

*EPA: eicosapentaenoic acid
DHA: docosahexaenoic acid

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